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Pediatric Postmarketing Pharmacovigilance Review

Date:	February 25, 2021
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Product Name:	Vimovo (naproxen/esomeprazole magnesium)
Pediatric Labeling Approval Date:	July 6, 2017
Application Type/Number:	NDA 022511
Applicant:	Horizon Medicines, LLC
OSE RCM #:	2020-1296

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vimovo (naproxen/esomeprazole magnesium) in pediatric patients from ages 0 through ≤ 17. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on adverse events associated with naproxen/esomeprazole magnesium in pediatric patients.

The FDA approved Vimovo (naproxen/esomeprazole magnesium) for adults on April 30, 2010 and for patients 12 years of age and older weighing at least 38 kilograms (kg) on July 6, 2017. Vimovo is a combination of naproxen, a non-steroidal anti-inflammatory drug (NSAID), and esomeprazole magnesium, a proton pump inhibitor (PPI). The naproxen component is indicated for relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults and for juvenile idiopathic arthritis (JIA) in adolescent patients 12 years of age and older weighing at least 38 kg. The esomeprazole magnesium component is indicated to decrease the risk of developing naproxen-associated gastric ulcers.

This review was triggered by the pediatric indication labeling change on July 6, 2017 approving naproxen/esomeprazole magnesium for use in adolescent patients 12 years of age and older weighing at least 38 kg with JIA.

DPV-I reviewed all U.S. FAERS reports with naproxen/esomeprazole magnesium use in the pediatric population (ages 0 through ≤ 17 years), received by FDA from the U.S. approval of Vimovo on April 30, 2010 through June 7, 2020.

DPV-I did not identify any pediatric safety concerns for naproxen/esomeprazole magnesium at this time. DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of naproxen/esomeprazole magnesium.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vimovo (naproxen/esomeprazole magnesium) in pediatric patients from ages 0 through ≤ 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on adverse events associated with naproxen/esomeprazole magnesium in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Vimovo is a combination of naproxen, a non-steroidal anti-inflammatory drug (NSAID), and esomeprazole magnesium, a proton pump inhibitor (PPI) indicated in adult and adolescent patients 12 years of age and older weighing at least 38 kg. The naproxen component is indicated for relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults and for juvenile idiopathic arthritis (JIA) in adolescent patients. The esomeprazole magnesium component is indicated to decrease the risk of developing naproxen-associated gastric ulcers.

FDA approved Vimovo for adults on April 30, 2010 and for patients 12 years of age and older weighing at least 38 kilograms (kg) on July 6, 2017. Vimovo is available in a delayed-release oral tablet in two strengths: 375 mg enteric-coated naproxen /20 mg immediate-release esomeprazole and 500 mg enteric-coated naproxen /20 mg immediate-release esomeprazole.[1]

Vimovo is a 505(b)(2) application using Nexium (esomeprazole magnesium) and EC Naprosyn (naproxen) as the reference listed drugs. EC-Naprosyn is approved in pediatric patients two years and older for polyarticular juvenile idiopathic arthritis.[2] Nexium is approved in pediatric patients 1 to 17 years of age for the short-term treatment of gastroesophageal reflux disease (GERD) as well as in pediatric patients 1 month to less than 1 year for the short-term treatment of erosive esophagitis due to acid-mediated GERD.[3] This pediatric approval of Vimovo is based on extrapolation of adequate and well-controlled studies in adults and supported by a 6-month safety study including pharmacokinetic assessment of naproxen and esomeprazole magnesium in 36 adolescent patients with JIA requiring treatment with NSAIDS. The study identified no new safety signals and the pharmacokinetics in this age group were determined to be similar to those of adults.[4]

DPV-I has not previously presented a naproxen/esomeprazole magnesium pediatric evaluation to the Pediatric Advisory Committee (PAC). This review was triggered by the pediatric indication labeling change on July 6, 2017 approving naproxen/esomeprazole magnesium for use in adolescent patients 12 years of age and older weighing at least 38 kg with JIA.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Vimovo labeling contains the following relevant safety information in the Prescribing Information.[1]

Reference ID: 4752840

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

▪ Non-Steroidal Anti-inflammatory Drugs (NSAIDs), a component of VIMOVO, cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see Warnings and Precautions (5.1)].

▪ VIMOVO is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4), and Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation

▪ NSAIDs, a component of VIMOVO cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see Warnings and Precautions (5.2)].

----------CONTRAINDICATIONS----------

• Known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any components of the drug product including omeprazole. (4)
• History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. (4)
• In the setting of coronary artery bypass graft (CABG) surgery. (4)
• In patients receiving rilpivirine-containing products. (4, 7)

----------WARNINGS AND PRECAUTIONS----------

• Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.3)
• Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.4, 7)
• Heart Failure and Edema: Avoid use of VIMOVO in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.5)
• Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of VIMOVO in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. (5.6)
• Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.7)
• Exacerbation of Asthma Related to Aspirin Sensitivity: VIMOVO is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
• Serious Skin Reactions: Discontinue VIMOVO at first appearance of skin rash or other signs of hypersensitivity. (5.9)

• Premature Closure of Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1) • Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs of symptoms of anemia. (5.11, 7)
• Masking of Inflammation and Fever: Potential for diminished utility of diagnostic signs in detecting infections. (5.12)
• Laboratory Monitoring: Obtain CBC and chemistry profile periodically during treatment. Monitor hemoglobin periodically in patients on long-term treatment who have an initial value of 10 g or less. (5.13)
• Active Bleeding: Withdraw treatment in patients who experience active and clinically significant bleeding. (5.14)
• Concomitant NSAID Use: Do not use VIMOVO with other naproxen containing products or other non-aspirin NSAIDs. (5.15)
• Gastric Malignancy: In adults, symptomatic response to esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.16)
• Acute Tubulointerstitial Nephritis: Discontinue treatment and evaluate patients. (5.17)
• Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk of Clostridium difficile associated diarrhea. (5.18)
• Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.19)
• Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous, new onset or exacerbation of existing disease; discontinue VIMOVO and refer to specialist for evaluation. (5.20)
• Interaction with Clopidogrel: Avoid concomitant use. (5.21, 7) • Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.22)
• Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.23)
• Interaction with St. John's Wort or Rifampin: Avoid concomitant use. (5.24, 7)
• Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia, enterochromaffin-like cell hyperplasia, and increased Chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.25)
• Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. (5.26, 7)
• Fundic Gland Polyps: Risk increases with long-term PPI use, especially beyond one year. Use the shortest duration of therapy. (5.27)

----------ADVERSE REACTIONS----------

Most common adverse reactions in clinical trials (>5%) are gastritis and diarrhea. (6.1)

----------USE IN SPECIFIC POPULATIONS----------

The safety and effectiveness of VIMOVO have been established in adolescent patients 12 years of age and older weighing at least 38 kg for the symptomatic relief of JIA and to decrease the risk of developing naproxen-associated gastric ulcers. Use of VIMOVO in this age group is based on extrapolation of adequate and well-controlled studies in adults and supported by a 6-month safety study including pharmacokinetic assessment of naproxen and esomeprazole magnesium in 36 adolescent patients with JIA. Based on the limited data, the plasma naproxen and plasma esomeprazole concentrations were found to be within the range to that observed to

those found in healthy adults. The safety profile of VIMOVO in adolescent patients with JIA was similar to adults with RA.

The safety and effectiveness of VIMOVO in pediatric patients less than 12 years of age or less than 38 kg with JIA have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	June 8, 2020
Time period of search	April 30, 2010† - June 7, 2020
Search type	Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredient: esomeprazole magnesium/ naproxen Product Name: Vimovo
MedDRA search terms (Version 22.1)	All Preferred Terms (PTs)
* See Appendix A for a description of the FAERS database. † Approval Date for Vimovo (naproxen/esomeprazole magnesium)	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from April 30, 2010 through June 7, 2020 with naproxen/esomeprazole magnesium.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From April 30, 2010 through June 7, 2020 with Naproxen/Esomeprazole Magnesium			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1,687 (1,376)	1,079 (770)	142 (134)
Pediatrics (0 - <17 years)	1 (1)	0 (0)	0 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.			

Reference ID: 4752840

3.1.2 Pediatric Case in FAERS (N=1)

Our FAERS search retrieved one non-serious pediatric report from April 30, 2010 through June 7, 2020. The case is summarized below.

Case# 16785052 (US, Direct): A consumer reported that a 16-year-old female experienced a pruritic rash after initiating therapy with naproxen/esomeprazole magnesium. The reporter listed no known medical conditions. After taking two naproxen/esomeprazole magnesium pills from a boxed sample obtained from a physician, the patient experienced an itchy rash under her chin. Naproxen/esomeprazole magnesium dose was not reported. The product was used 33 days after the manufacturer's expiration date. The rash was not initially attributed to naproxen/esomeprazole magnesium and a third pill was administered. Within 3 hours of administration of the third pill the rash intensified and spread to cheeks, arms, underarms, and legs. Naproxen/esomeprazole magnesium was discontinued and the rash improved with occasional new spots appearing for about 2 more weeks.

Reviewer's Comments: The current naproxen/esomeprazole magnesium labeling contains language regarding Serious Skin Reactions with direction to discontinue use at the appearance of a skin rash in WARNING AND PRECAUTIONS, Subsection 5.9 Serious Skin Reactions.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports.

4 DISCUSSION

DPV-I reviewed all FAERS reports with naproxen/esomeprazole magnesium use in the pediatric population (ages 0 through ≤ 17 years), received by FDA from the U.S. approval of Vimovo on April 30, 2010 through June 7, 2020. DPV-I identified one non-serious U.S. pediatric case describing a patient who developed a rash after initiation of therapy with naproxen/esomeprazole magnesium; no long-term sequela was reported after drug discontinuation. Rash is a labeled event for naproxen/esomeprazole magnesium.

Our review of FAERS for pediatric reports of adverse events identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with naproxen/esomeprazole magnesium.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns for naproxen/esomeprazole magnesium at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of naproxen/esomeprazole magnesium.

7 REFERENCES

1) Vimovo (naproxen and esomeprazole magnesium) [Prescribing Information]. Lake Forest, IL: Horizon Medicines, LLC. November 2020.

2) EC-Naprosyn (naproxen delayed-release) [Prescribing Information]. Essex, United Kingdom: Atnahs Pharma US Limited. November 2019.

3) Nexium (esomeprazole magnesium) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. November 2020.

4) Korvick J. Summary Review for Regulatory Action. Deputy Division Director Summary Review. NDA 22511 Supplement 019. Vimovo (naproxen and esomeprazole magnesium). July 6, 2017.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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