HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIMOVO safely and effectively. See full prescribing information for VIMOVO.

VIMOVO® (naproxen and esomeprazole magnesium) delayed-release tablets, for oral use
Initial US Approval: 2010

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) 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. (5.1)**
- **VIMOVO is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **NSAIDs, including naproxen, 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. (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	5/2016
Dosage and Administration (2)	5/2016
Contraindications (4)	5/2016
Warnings and Precautions, Cardiovascular Thrombotic Events (5.1)	5/2016
Warnings and Precautions, Gastrointestinal Bleeding, Ulceration, And Perforation (5.2)	5/2016
Warnings and Precautions, Atrophic Gastritis (5.17), removed	10/2016
Warnings and Precautions, Cutaneous and Systemic Lupus Erythematosus (5.20)	10/2016

----------INDICATIONS AND USAGE----------
VIMOVO is a fixed combination of naproxen, a non-steroidal anti-inflammatory drug, and esomeprazole, a proton pump inhibitor (PPI) indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers. (1)
Limitations of Use:

- VIMOVO is not interchangeable with the individual components of naproxen and esomeprazole magnesium. (1)

----------DOSAGE AND ADMINISTRATION----------
One tablet twice daily. Should be avoided in moderate/severe renal insufficiency or in severe hepatic insufficiency. Consider dose reduction in mild/moderate hepatic insufficiency. (2)

- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2).

----------DOSAGE FORMS AND STRENGTHS----------
VIMOVO delayed-release tablets (3):

- 375 mg enteric-coated naproxen /20 mg immediate-release esomeprazole magnesium
- 500 mg enteric-coated naproxen /20 mg immediate-release esomeprazole magnesium.

----------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)

----------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 Fetal 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 Interstitial Nephritis: Observed in patients taking PPIs. (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)

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

To report SUSPECTED ADVERSE REACTIONS, contact Horizon Pharma USA, Inc. at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
See full prescribing information for a list of clinically important drug interactions. (7)

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

- Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation. (5.10, 8.1)

- Females and Males of Reproductive Potential: NSAIDs are associated with reversible infertility. Consider withdrawal of VIMOVO in women who have difficulties conceiving. (8.3)

SEE 17 FOR PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide

Revised October 2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

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)]*.**

1 INDICATIONS AND USAGE

VIMOVO is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. 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. Controlled studies do not extend beyond 6 months.

Limitations of Use:
VIMOVO is not interchangeable with the individual components of naproxen and esomeprazole magnesium.

2 DOSAGE AND ADMINISTRATION

Use the lowest dose for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5.1)]*. Carefully consider the potential benefits and risks of VIMOVO and other treatment options before deciding to use VIMOVO. VIMOVO does not allow for administration of a lower daily dose of esomeprazole. If a dose of esomeprazole lower than a total daily dose of 40 mg is more appropriate, a different treatment should be considered.

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis
The dosage is one tablet twice daily of VIMOVO 375 mg naproxen and 20 mg of esomeprazole or 500 mg naproxen and 20 mg of esomeprazole.

The tablets are to be swallowed whole with liquid. Do not split, chew, crush or dissolve the tablet. VIMOVO is to be taken at least 30 minutes before meals.

Geriatric Patients
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Use caution when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly use the lowest effective dose *[see Use in Specific Populations (8.5)* and *Clinical Pharmacology (12.3)]*.

Patients with Moderate to Severe Renal Impairment
Naproxen-containing products are not recommended for use in patients with moderate to severe or severe renal impairment (creatinine clearance <30 mL/min) *[see Warnings and Precautions (5.6)* and *Use in Specific Populations (8.7)]*.

Hepatic Insufficiency
Monitor patients with mild to moderate hepatic impairment closely and consider a possible dose reduction based on the naproxen component of VIMOVO.

VIMOVO should be avoided in patients with severe hepatic impairment *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6)]*.

Pediatric Patients
The safety and efficacy of VIMOVO in children younger than 18 years has not been established. VIMOVO is therefore not recommended for use in children.

3 DOSAGE FORMS AND STRENGTHS
VIMOVO is an oval, yellow, delayed-release tablets for oral administration containing either:
- 375 mg enteric-coated naproxen and 20 mg immediate-release esomeprazole magnesium tablets printed with 375/20 in black, or
- 500 mg enteric-coated naproxen and 20 mg immediate-release esomeprazole magnesium tablets printed with 500/20 in black.

4 CONTRAINDICATIONS
VIMOVO is contraindicated in the following patients:
- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any components of the drug product, including omeprazole. Hypersensitivity reactions to esomeprazole may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria *[see Warnings and Precautions (5.7, 5.8, 5.9, 5.17) and Postmarketing Experience (6.2)]*.
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.7, 5.8)]*.
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI), and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDS. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of

previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions (5.2)]*.

Status Post Coronary Artery Bypass Graft (CABG) Surgery
Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]*.

Post-MI Patients
Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years after follow-up.

Avoid the use of VIMOVO in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If VIMOVO is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including naproxen, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events are in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such as patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.

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