

## 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)

### INDICATIONS AND USAGE

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, requiring naproxen for symptomatic relief of arthritis and esomeprazole magnesium to decrease the risk of developing naproxen-associated gastric ulcers.

The naproxen component of VIMOVO is indicated for relief of signs and symptoms of:

- osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults.
- juvenile idiopathic arthritis (JIA) in adolescent patients.

The esomeprazole magnesium component of VIMOVO is indicated to decrease the risk of developing naproxen-associated gastric ulcers. (1)

### Limitations of Use:

- Do not substitute VIMOVO with the single-ingredient products of naproxen and esomeprazole magnesium. (1)
- 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. (1)
- Controlled studies do not extend beyond 6 months. (1)

### DOSAGE AND ADMINISTRATION

#### Administration

- Use the lowest naproxen dose for the shortest duration consistent with individual patient treatment goals. (2.1, 5.1).
- If a total daily dose of less than 40 mg esomeprazole is more appropriate, a different treatment should be considered. (2.1)
- Swallow VIMOVO tablets whole with liquid at least 30 minutes before meals. (2.1)

#### Recommended Dosage (2.2)

Adolescents 12 years of age and older weighing 38 kg to less than 50 kg:  
One VIMOVO tablet twice daily of 375 mg naproxen/20 mg of esomeprazole

Adults and adolescents 12 years of age and older greater than 50 kg:

- One VIMOVO tablet twice daily of either:
- 375 mg naproxen/20 mg of esomeprazole; or
  - 500 mg of naproxen/20 mg of esomeprazole

#### Renal or Hepatic Impairment (2.3)

- Avoid in moderate/severe renal impairment or severe hepatic impairment.
- Consider dose reduction in mild/moderate hepatic impairment.

### DOSAGE FORMS AND STRENGTHS

VIMOVO delayed-release tablets (3):

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

### 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 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)
- **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)

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

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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, a combination of naproxen and esomeprazole magnesium, is indicated in adult and adolescent patients 12 years of age and older weighing at least 38 kg, requiring naproxen for symptomatic relief of arthritis and esomeprazole magnesium to decrease the risk for developing naproxen-associated gastric ulcers.

The naproxen component of VIMOVO is indicated for relief of signs and symptoms of:

- osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults.
- juvenile idiopathic arthritis (JIA) in adolescent patients.

The esomeprazole magnesium component of VIMOVO is indicated to decrease the risk of developing naproxen-associated gastric ulcers.

#### Limitations of Use:

- Do not substitute VIMOVO with the single-ingredient products of naproxen and esomeprazole magnesium.
- 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 [see *Use in Specific Populations (8.4)*, *Clinical Studies (14)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

- Use the lowest naproxen 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 magnesium. If a total daily dose of less than 40 mg esomeprazole is more appropriate, a different treatment should be considered.

- Swallow VIMOVO tablets whole with liquid. Do not split, chew, crush or dissolve the tablet. Take VIMOVO at least 30 minutes before meals.
- Patients should be instructed that if a dose is missed, it should be taken as soon as possible. However, if the next scheduled dose is due, the patient should not take the missed dose, and should be instructed to take the next dose on time. Patients should be instructed not to take 2 doses at one time to make up for a missed dose.
- Antacids may be used while taking VIMOVO.

## 2.2 Recommended Dosage

The recommended dosage of VIMOVO by indication is shown in the table:

Indication	Patient Population	Recommended Dosage
Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis	Adults	One VIMOVO tablet twice daily of either: 375 mg naproxen/20 mg of esomeprazole; or 500 mg naproxen/20 mg of esomeprazole
Juvenile Idiopathic Arthritis in Adolescent Patients 12 Years of Age and Older and Weighing at Least 38 kg	Greater than 50 kg	
		38 kg to less than 50 kg

## 2.3 Use in Renal Impairment or Hepatic Impairment

### Renal Impairment

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

### Hepatic Impairment

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)*].

## 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 tablets printed with 375/20 in black, or
- 500 mg enteric-coated naproxen and 20 mg immediate-release esomeprazole 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)*, *Adverse Reactions (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)*].
- Proton pump inhibitors (PPIs), including esomeprazole magnesium, are contraindicated in patients receiving rilpivirine-containing products [*see Drug Interactions (7)*].

## 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,

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