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
Initial US Approval: 2010

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

See full prescribing information for complete boxed warning

Cardiovascular Risk

- **Naproxen, a component of VIMOVO, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. *(5.1)***
- **VIMOVO is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. *(4, 5.1)***

Gastrointestinal Risk

- **NSAIDs, including naproxen, a component of VIMOVO, cause an increased risk of serious gastrointestinal 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 are at greater risk for serious gastrointestinal (GI) events. *(5.4)***

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

Warnings and Precautions, Hypomagnesemia (5.19)	05/2011
Warnings and Precautions, Concomitant use of St John's Wort or Rifampin with VIMOVO (5.20)	06/2011
Warnings and Precautions, Bone Fracture (5.16)	11/2011
Warnings and Precautions, Concomitant use of VIMOVO with Methotrexate (5.21)	01/2012

----------INDICATIONS AND USAGE----------

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)

----------DOSAGE AND ADMINISTRATION----------

One tablet twice daily. Use the lowest effective dose. Should be avoided in moderate/severe renal insufficiency or in severe hepatic insufficiency. Consider dose reduction in mild/moderate hepatic insufficiency (2)

----------DOSAGE FORMS AND STRENGTHS----------

Delayed release tablets: 375 mg/20 mg or 500 mg/20 mg of naproxen and esomeprazole magnesium (3)

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

- Known hypersensitivity to any component of VIMOVO or substituted benzimidazoles (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4, 5.8, 5.9, 5.13)
- Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)
- Late pregnancy (4, 5.10, 8.1)

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

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Patients with known CV disease/risk factors may be at greater risk (5.1)
- Serious gastrointestinal (GI) adverse events, which can be fatal. The risk is greater in patients with a prior history of ulcer disease or GI bleeding, and in patients at high risk for GI events, especially the elderly. VIMOVO should be used with caution in these patients (5.4, 8.5)
- Treatment should be withdrawn when active and clinically significant bleeding from any source occurs (5.5)
- Elevated liver enzymes and, rarely, severe hepatic reactions. Discontinue use immediately if abnormal liver enzymes persist or worsen (5.11, 8.6, 12.3)
- Should be avoided in patients with severe hepatic impairment (e.g., Childs-Pugh C)
- New onset or worsening of pre-existing hypertension. Blood pressure should be monitored closely during treatment with VIMOVO (5.2, 7.1, 7.4)
- Congestive heart failure and edema. VIMOVO should be used with caution in patients with fluid retention or heart failure (5.3)
- Renal papillary necrosis and other renal injury with long-term use. Use VIMOVO with caution in the elderly, those with impaired renal function, hypovolemia, salt depletion, heart failure, liver dysfunction, and those taking diuretics, or ACE-inhibitors. Not recommended for patients with moderate or severe renal impairment (2, 5.6, 5.7, 7.1, 7.4, 8.7)
- Anaphylactic reactions. Do not use VIMOVO in patients with the aspirin triad (5.8)
- Serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal and can occur without warning. Discontinue VIMOVO at first appearance of skin rash or any other sign of hypersensitivity (5.9)
- Long-term and multiple daily dose PPI therapy is associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine (5.16)
- Symptomatic response to esomeprazole does not preclude the presence of gastric malignancy (5.4)
- Atrophic gastritis has been noted on biopsy with long-term omeprazole therapy (5.4)
- 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. (5.18)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.19)
- Avoid concomitant use of VIMOVO with St John's Wort or rifampin due to the potential reduction in esomeprazole levels. (5.20, 7.16)

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

Most common adverse reactions in clinical trials (>5%): erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Concomitant use of NSAIDs may reduce the antihypertensive effect of ACE Inhibitors, diuretics, and beta-blockers (7.1, 7.4, 7.9)
- Concomitant use of NSAIDs increases lithium plasma levels (7.5)
- Methotrexate: VIMOVO may increase serum levels of methotrexate (7.8)
- Concomitant use of VIMOVO with warfarin may result in increased risk of bleeding complications. Monitor for increases in INR and prothrombin time (7.7)
- Esomeprazole inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts and digoxin). Patients treated with VIMOVO and digoxin may need to be monitored for increases in digoxin toxicity (7.12)
- As with all NSAIDs caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity. (7.4)
- Tacrolimus: Concomitant administration of esomeprazole, a component of VIMOVO, and tacrolimus may increase the serum levels of tacrolimus. (7.5)

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

- Pregnancy Category C: VIMOVO should not be used in late pregnancy (4, 5.10, 8.1)
- Hepatic Insufficiency: VIMOVO should be avoided in patients with severe hepatic insufficiency (2, 4, 5.11, 8.6, 12.3)
- Renal Insufficiency: VIMOVO is not recommended in patients with moderate or severe renal insufficiency (2, 5.6, 5.7, 8.7, 12.3)

SEE 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised JANUARY 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

Cardiovascular Risk

- Non-Steroidal Anti-inflammatory Drugs (NSAIDs), a component of VIMOVO, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see *Warnings and Precautions (5.1)*].
- VIMOVO is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Contraindications (4)*, and *Warnings and Precautions (5.1)*].

Gastrointestinal Risk

- NSAIDs, including naproxen, a component of VIMOVO, cause an increased risk of serious gastrointestinal 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 are at greater risk for serious gastrointestinal events [see *Warnings and Precautions (5.4)*].

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.

2 DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of VIMOVO and other treatment options before deciding to use VIMOVO. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. 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, 5.7)* 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 (5.11), Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

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

Oval, yellow, delayed release tablets for oral administration containing either:

- 375 mg enteric coated naproxen and 20 mg esomeprazole (as magnesium trihydrate) tablets printed with 375/20 in black, or
- 500 mg enteric coated naproxen and 20 mg esomeprazole (as magnesium trihydrate) tablets printed with 500/20 in black.

4 CONTRAINDICATIONS

VIMOVO is contraindicated in patients with known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any of the excipients.

VIMOVO is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients [see *Warnings and Precautions (5.8, 5.13)*]. Hypersensitivity reactions, eg, angioedema and anaphylactic reaction/shock, have been reported with esomeprazole use.

VIMOVO is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions (5.1)*].

VIMOVO is contraindicated in patients in the late stages of pregnancy [see *Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)*].

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, myocardial infarction, and stroke, which can be fatal. All NSAIDS, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the

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