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.

SLE is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving VIMOVO, discontinue drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

5.21 Interaction with Clopidogrel

Avoid concomitant use of esomeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole, a component of VIMOVO, consider alternative anti-platelet therapy *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

5.22 Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo-or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

5.23 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically *[see Adverse Reactions (6.2)]*.

5.24 Concomitant use of St. John's Wort or Rifampin with VIMOVO

Drugs that induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of VIMOVO with St. John's Wort or rifampin *[see Drug Interactions (7)]*.

5.25 Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary *[see Drug Interactions (7), Clinical Pharmacology (12.2)]*.

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help *[see Contraindications (4) and Warnings and Precautions (5.7)]*.

Serious Skin Reactions
Advise patients to stop VIMOVO immediately if they develop any type of rash and contact their health care provider as soon as possible *[see Warnings and Precautions (5.9)]*.

Fetal Toxicity
Inform pregnant women to avoid use of VIMOVO and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closure of the fetal ductus arteriosus *[see Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)]*.

Infertility
Advise females of reproductive potential that NSAIDs, including VIMOVO, may be associated with reversible infertility *[see Use in Specific Populations (8.3)]*.

Gastric Malignancy
To return to their healthcare provider if they have a gastric symptoms while taking VIMOVO or after completing treatment *[see Warnings and Precautions (5.7)]*.

Acute Interstitial Nephritis
Advise patients to report to their health care provider if they experience a decrease in the amount they urinate or have blood in their urine *[see Warnings and Precautions (5.17)]*.

Clostridium difficile-Associated Diarrhea
Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea *[see Warnings and Precautions (5.18)]*.

Bone Fracture
Advise patients to report any sign or symptom of osteoporosis (e.g., recent bone fracture, low bone density) to their health care provider *[see Warnings and Precautions (5.19)]*.

Cutaneous and Systemic Lupus Erythematosus
Advise patients to immediately call their healthcare provider any new or worsening of symptoms associated with cutaneous or systemic lupus erythematosus *[see Warnings and Precautions (5.20)]*.

Cyanocobalamin (Vitamin B-12) Deficiency
Advise patients taking VIMOVO for long periods of time, to report to their healthcare provider if they experience weakness, tiredness, or light-headedness or rapid heartbeat and breathing or pale skin *[see Warnings and Precautions (5.22)]*.

Hypomagnesemia
Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia *[see Warnings and Precautions (5.23)]*.

Drug Interactions
- Inform patients that the concomitant use of VIMOVO with other NSAIDs or salicylates (e.g., diflunisal, salsalate) it is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy *[see Warnings and*

Precautions (5.15), Drug Interactions (7)]. Alert patients that NSAIDs may be present in the "over the counter" medications for treatment of colds, fever or insomnia.

- Advise patients to report to their healthcare provider if they start treatment with clopidogrel, St. John's Wort or rifampin; or, if they take high-dose methotrexate *[see Warnings and Precautions (5.21, 5.24, 5.26)]*.
- Inform patients not to use low-dose aspirin concomitantly with VIMOVO until they talk to their health care provider *[see Drug Interactions (7)]*.

Administration

- Inform patients that VIMOVO tablets should be swallowed whole with liquid. Tablets should not be split, chewed, crushed or dissolved. VIMOVO tablets should be taken at least 30 minutes before meals *[see Dosage and Administration (2)]*.
- 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.
- Inform patients that antacids may be used while taking VIMOVO.

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Medication Guide
VIMOVO (vi-moh-voh)
(naproxen and esomeprazole magnesium)
delayed-release tablets

What is the most important information I should know about VIMOVO?

You should take VIMOVO exactly as prescribed, at the lowest dose possible and for the shortest time needed.

VIMOVO may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your healthcare provider.

VIMOVO contains naproxen, a nonsteroidal anti-inflammatory drug (NSAID) and esomeprazole magnesium, a proton pump inhibitor (PPI) medicine.

VIMOVO can cause serious side effects including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take VIMOVO right before or after a heart surgery called a "coronary artery bypass graft (CABG)."
  Avoid taking VIMOVO after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

  Talk to your healthcare provider or pharmacist before using other medicines that contain NSAIDs, including low-dose aspirin, during treatment with VIMOVO. Some NSAIDs are sold in lower doses without a prescription (over-the-counter).
- **A type of kidney problem (acute interstitial nephritis).** Some people who take proton pump inhibitor (PPI) medicines, including VIMOVO, may develop a kidney problem called acute interstitial nephritis that can happen at any time during treatment with VIMOVO. Call your healthcare provider right away if you have a decrease in the amount that you urinate or if you have blood in your urine.
- **Diarrhea caused by an infection (*Clostridium difficile*) in your intestines.** Call your healthcare provider right away if you have watery stools or stomach pain that does not go away. You may or may not have a fever.
- **Bone fractures (hip, wrist, or spine).** Bone fractures in the hip, wrist, or spine may happen in people who take multiple daily doses of PPI medicines and for a long period of time (a year or longer). Tell your healthcare provider if you have a bone fracture, especially in the hip, wrist, or spine.
- **Certain types of lupus erythematosus.** Lupus erythematosus is an autoimmune disorder (the body's immune cells attack other cells or organs in the body). Some people who take PPI medicines, including VIMOVO, may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your healthcare provider right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

Talk to your healthcare provider about your risk of these serious side effects.

VIMOVO can have other serious side effects. See **"What are the possible side effects of VIMOVO?"**

What is VIMOVO?

VIMOVO is a prescription medicine used in adults and adolescents, 12 years of age and older who weigh at least 84 pounds (38 kg), who need to take naproxen for relief of symptoms of arthritis and who also need to decrease the risk of developing stomach ulcers caused by naproxen.

The naproxen in VIMOVO is used for the relief of signs and symptoms of:

- osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in adults
- juvenile idiopathic arthritis (JIA) in adolescents

The esomeprazole magnesium in VIMOVO is used to:

- decrease the risk of developing stomach ulcers in people who are taking naproxen

It is not known if VIMOVO is safe and effective in children less than 12 years of age or who weigh less than 84 pounds (38 kg).

You should not take a naproxen tablet and an esomeprazole magnesium tablet together instead of taking VIMOVO, because they will not work the same way.

Studies in people who take VIMOVO have not extended past 6 months.

Do not take VIMOVO:

- if you are allergic to naproxen, esomeprazole magnesium, omeprazole, any other PPI medicine, or any of the ingredients in VIMOVO. See the end of this Medication Guide for a complete list of ingredients in VIMOVO.

- if you have had an asthma attack, hives, or other allergic reaction after taking aspirin or any other NSAIDs.
- right before or after heart bypass surgery.
- if you are taking a medicine that contains rilpivirine (Edurant, Complera, Odefsey) used to treat HIV-1 (Human Immunodeficiency Virus).

Before taking VIMOVO, tell your healthcare provider about all of your medical conditions, including if you:

- have liver, kidney, or heart problems.
- have high blood pressure.
- have asthma.
- have low magnesium levels in your blood.
- have ulcerative colitis or Crohn's disease (inflammatory bowel disease or IBD).
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking VIMOVO during pregnancy. **You should not take VIMOVO after 29 weeks of pregnancy.**
- are breastfeeding or plan to breastfeed. The naproxen in VIMOVO can pass into your breast milk. It is not known if VIMOVO will harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take VIMOVO.
- are a female who can become pregnant. VIMOVO may be related to infertility in some women that is reversible when treatment with VIMOVO is stopped.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VIMOVO and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first**.

Especially tell your healthcare provider if you take:

- steroid hormones (corticosteroids)
- St. John's Wort
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)
- medicine for high blood pressure or heart problems
- a water pill (diuretic)
- aspirin
- antidepressant medicine
- medicine used to reduce the risk of blood clots, such as warfarin (Coumadin, Jantoven)
- methotrexate (Otrexup, Rasuvo, Trexall, Xatmep)
- digoxin (Lanoxin)
- clopidogrel (Plavix)

How should I take VIMOVO?

- Take VIMOVO exactly as prescribed by your healthcare provider.
- Take 1 VIMOVO tablet 2 times each day.
- Take VIMOVO at least 30 minutes before a meal.
- Swallow VIMOVO tablets whole with liquid. Do not split, chew, crush or dissolve VIMOVO.
- You may use antacids while taking VIMOVO.
- If you forget to take your dose of VIMOVO, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take 2 doses at one time to make up for a missed dose.
- If you take too much VIMOVO, call your healthcare provider or your poison control center at 1-800-222-1222 right away or go to the nearest emergency room.

What are the possible side effects of VIMOVO?

VIMOVO can cause serious side effects, including:

See **"What is the most important information I should know about VIMOVO?"**

- liver problems, including liver failure.
- new or worsening high blood pressure.
- heart failure.
- kidney problems, including kidney failure.
- life-threatening allergic reactions.
- asthma attacks in people who have asthma.
- life-threatening skin reactions.
- low red blood cells (anemia).
- hiding (masking) symptoms of an infection, such as swelling and fever.
- **Low vitamin B-12 levels** in your body can happen in people who have taken VIMOVO for a long time (more than 3 years). Tell your healthcare provider if you have symptoms of low vitamin B-12 levels, including shortness of breath, lightheadedness, irregular heartbeat, muscle weakness, pale skin, feeling tired, mood changes, and tingling or numbness in the arms or legs.
- **Low magnesium levels** in your body can happen in people who have taken VIMOVO for at least 3 months**.** Tell your healthcare provider if you have symptoms of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hands, feet or voice.
- **Stomach growths (fundic gland polyps)** People who take PPI medicines for a long time have an increased risk of developing a certain type of stomach growths called fundic gland polyps, especially after taking PPI medicines for more than 1 year.

The most common side effects of VIMOVO include: inflammation of the lining of the stomach and diarrhea

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking VIMOVO and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands, and feet

If you take too much VIMOVO, call your healthcare provider or get medical help right away.

These are not all the possible side effects of VIMOVO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIMOVO?

- Store VIMOVO at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Store VIMOVO in the original container.
- Keep the bottle of VIMOVO tightly closed to protect from moisture.

Keep VIMOVO and all medicines out of the reach of children.

What are the ingredients in VIMOVO?

Active ingredients: naproxen and esomeprazole magnesium

Inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, glyceryl monostearate, hypromellose, iron oxide black, magnesium stearate, methacrylic acid copolymer dispersion, methylparaben, polysorbate 80, polydextrose, polyethylene glycol, povidone, propylene glycol, propylparaben, titanium dioxide, and triethyl citrate

General information about the safe and effective use of VIMOVO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIMOVO for a condition for which it was not prescribed. Do not give VIMOVO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about VIMOVO that is written for health professionals.

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For more information, go to www.VIMOVO.com or call 1-866-479-6742.
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