

Vimovo™ Monograph

Brand Name: Vimovo™

Generic Name: Naproxen/Esomeprazole

Manufacturer: AstraZeneca

Year Introduced: April 30, 2010

Mechanisms of Action:¹⁻²

Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase in the gastric parietal cell. Esomeprazole is protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

FDA Approved Indications:¹⁻²

This combination product is indicated for 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 Non-Steroidal Anti-inflammatory Drug (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.

Contraindications:¹⁻²

- Patients with known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any of the excipients
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs
- Perioperative pain in the setting of CABG surgery

- Patients in the late stages of pregnancy

Pharmacokinetics:¹⁻²

	Naproxen	Esomeprazole
<i>Absorption:</i>	95% bioavailability; peak plasma levels reached in ~3 hours	64-90% bioavailability; mean C _{max} occurring 0.43 - 1.2 hours
<i>Protein Binding:</i>	Greater than 99% albumin-bound	97% bound to plasma proteins
<i>Metabolism:</i>	Hepatic; CYP2C9, CYP1A2	Hepatic; CYP2C19, CYP3A4
<i>Elimination:</i>	Urine (95%), Feces (≤3%)	Urine (80%), Feces (20%)
<i>Half-life:</i>	~15 hours	< 1 hour

C_{max} = maximum plasma concentration

A **xerox** Company**Adverse Effects (%):¹⁻²**

Body System	Vimovo 500mg/20mg BID (N=428)	Naproxen EC 500mg BID (N=426)
GI Disorders		
Gastritis Erosive	19	38
Dyspepsia	18	27
Gastritis	17	14
Diarrhea	6	5
Gastric Ulcer	6	24
Abdominal Pain Upper	6	9
Nausea	5	5
Hiatus Hernia	4	6
Abdominal Distention	4	4
Flatulence	4	3
Esophagitis	4	8
Constipation	3	3
Abdominal Pain	2	2
Erosive Duodenitis	2	12
Abdominal Pain Lower	2	3
Duodenitis	1	7
Gastritis Hemorrhagic	1	2
Gastroesophageal Reflux Disease	<1	4
Duodenal Ulcer	<1	5
Erosive Esophagitis	<1	6
Infections and Infestations		
Upper Respiratory Tract Infection	5	4
Bronchitis	2	2
Urinary Tract Infection	2	1
Sinusitis	2	2
Nasopharyngitis	<1	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1	2
Nervous System Disorders		
Headache	3	1
Dysgeusia	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	2	3

Body System	Vimovo 500mg/20mg BID (N=490)	Placebo (N=246)
GI Disorders		
Dyspepsia	8	12
Diarrhea	6	4
Abdominal Pain Upper	4	3
Constipation	4	1
Nausea	4	4
Nervous System Disorders		
Dizziness	3	2
Headache	3	5
General Disorders / Administration		
Site Conditions		
Peripheral Edema	3	1
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	1	3
Infections and Infestations		
Sinusitis	2	2

Drug Interactions:¹⁻²

Precipitant Drug	Object Drug		Description
NSAIDs	ACE inhibitors	↑	NSAIDs may diminish anti-hypertensive effect of ACE inhibitors.
Naproxen	Aspirin	↓	Naproxen given concomitantly with aspirin decreases protein binding of aspirin; may increase risk of serious adverse events.
Naproxen	Cholestyramine	↓	Cholestyramine can delay absorption of Naproxen
NSAIDs	Diuretics	↓	NSAIDs may reduce natriuretic effect of furosemide and thiazides
Naproxen	Lithium	↑	NSAIDs may increase in lithium levels (15%) and decrease renal clearance (20%)
NSAIDs	Methotrexate	↑	May increase methotrexate

Precipitant Drug	Object Drug		Description
			toxicity
Naproxen	Anticoagulants	↑	Naproxen decreases platelet aggregation; may prolong bleeding time and increase risk of serious GI bleeding when given drugs given together.
NSAIDs	SSRIs	↑	Increased risk of GI bleeding
Naproxen	Highly protein bound drugs	↑↓	Theoretical potential for interaction with highly protein bound drugs such as hydantoin, sulfonamides, sulfonylureas
Naproxen	Beta Blockers, Propranolol	↓	Can reduce antihypertensive effect
Probenecid	Naproxen	↑	May increase Naproxen plasma levels and extend half-life significantly
Esomeprazole	pH dependent drugs	↑↓	May interfere with absorption of drugs where gastric pH is an important determinant of bioavailability (ketoconazole, iron salts, digoxin)
Omeprazole, PPIs	Antiretroviral Agents	↑↓	PPIs substantially decrease atazanavir plasma levels and decrease therapeutic effect.; possible increased atazanavir absorption. Omeprazole may increase saquinavir levels
Esomeprazole	Diazepam	↓	May decrease diazepam clearance (45%)
Esomeprazole	Cilostazol	↑	Increase concentrations of cilostazol and metabolite (dose reduction of cilostazol required)
CYP2C19, CYP3A4 Inhibitors	Esomeprazole	↑	CYP2C19 and CYP3A4 inhibitors such as voriconazole may more than

Precipitant Drug	Object Drug	Description
		double esomeprazole exposure

Precaution/Warnings:¹⁻²

- **Cardiovascular Thrombotic Events:** 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.
- **Hypertension:** NSAIDs, including naproxen, a component of VIMOVO, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs
- **Congestive Heart Failure and Edema:** Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs and should be used with caution in patients with fluid retention, or heart failure
- **Gastrointestinal Effects:** NSAIDs, including naproxen, a component of VIMOVO, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the 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. NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated
- **Active Bleeding:** When active and clinically significant bleeding from any source occurs in patients receiving Vimovo, the treatment should be withdrawn.
- **Renal Effects:** Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly

- **Advanced Renal Disease:** Treatment with Vimovo is not recommended in these patients with advanced renal disease, No information is available from controlled clinical studies regarding use in patients with advanced renal disease
- **Anaphylactoid Reactions:** Anaphylactoid reactions may occur in patients without known prior exposure to either component of Vimovo. NSAIDs should not be given to patients with the aspirin triad. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.
- **Skin Reactions:** NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning
- **Pregnancy:** In late pregnancy, as with other NSAIDs, naproxen, a component of Vimovo should be avoided because it may cause premature closure of the ductus arteriosus.
- **Hepatic Effects:** Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including naproxen, a component of Vimovo. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable elevations of ALT or AST (approximately $\geq 3x$ ULN) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported. Chronic alcoholic liver disease and probably other diseases with decreased or abnormal albumin reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. Vimovo is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed.
- **Hematologic Effects:** Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible.
- **Pre-existing Asthma:** Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin

and other NSAIDs has been reported in such aspirin-sensitive patients, Vimovo should not be administered to patients with this form of aspirin sensitivity

- **Concomitant NSAID Use:** Vimovo contains naproxen as one of its active ingredients. It should not be used with other naproxen-containing products since they all circulate in the plasma as the naproxen anion
- **Corticosteroid Treatment:** Vimovo cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
- **Bone Fracture:** Several studies and literature reports indicate that PPI therapy is associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
- **Masking of Inflammation and Fever:** The pharmacological activity of Vimovo in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.
- **Laboratory Tests:** Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

Pregnancy/Lactation:¹⁻²

- < 30 weeks gestation: Category C
- ≥ 30 weeks gestation: Category C
- The Naproxen anion has been found in the milk of lactating women; it is not known whether esomeprazole is excreted in human breast milk. Use of the combination should be avoided in nursing mothers.

Usual Dosage:¹⁻²

One tablet is to be taken twice daily at least 30 minutes before meals. Tablets are to be swallowed whole with liquid; do not split, crush, chew, or dissolve. Vimovo is not recommended for patients with moderate to severe renal impairment (CrCL < 30mL/min) or patients with severe hepatic impairment.

Availability:¹⁻²

Delayed release tablets: 375mg/20mg, 500mg/20mg

Clinical Studies:

Title & Author	Study Design	Results
Scheinman JM, et al. ³ (2006)	Randomized, double-blind, placebo-controlled, multicenter	<p><u>Venus</u> Endpoints:</p> <ul style="list-style-type: none"> Development of ulcers over 6 month period <p>Efficacy: esomeprazole 40 mg ≤ esomeprazole 20 mg < placebo</p> <ul style="list-style-type: none"> 4.7% esomeprazole 40 mg (p < 0.0001), 5.3% esomeprazole 20 mg (p < 0.001), and 20.4% placebo <p>Safety: esomeprazole 40 mg = esomeprazole 20 mg < placebo</p> <p><u>Pluto</u> Endpoints:</p> <ul style="list-style-type: none"> Development of ulcers over 6 month period <p>Efficacy: esomeprazole 40 mg ≤ esomeprazole 20 mg < placebo</p> <ul style="list-style-type: none"> 4.4% esomeprazole 40 mg (p = 0.007), 5.2% esomeprazole 20 mg (p = 0.018), and 12.3% placebo Significant reductions were observed for users of both non-selective NSAIDs and COX-2 inhibitors <p>Safety: esomeprazole 40 mg = esomeprazole 20 mg > placebo</p> <p><u>Pooled analysis for patients using COX-2 Inhibitors (n = 400)</u> Endpoints:</p> <ul style="list-style-type: none"> Development of ulcers over 6 month period <p>Efficacy: esomeprazole 20 mg < esomeprazole 40 mg < placebo</p> <ul style="list-style-type: none"> 0.9% on esomeprazole 20 mg (p < 0.001), 4.1% esomeprazole 40 mg (p = 0.002) and 16.5% placebo <p>Safety: esomeprazole 40 mg = esomeprazole 20 mg < placebo</p>

Title & Author	Study Design	Results
		<p>Conclusion: For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs including COX-2 inhibitors</p>

Summary:

Vimovo contains the NSAID naproxen and the proton pump inhibitor esomeprazole. Naproxen and other NSAIDs are widely used for the relief of pain and inflammation associated with arthritis and other musculoskeletal disorders. However, the benefit of these drugs is not without the risk of developing serious, life-threatening ulcer complications. With the advent of proton pump inhibitors, more profound acid suppression has been reported as being associated with the acceleration of ulcer healing and prevention of ulcer relapse among long-term users of NSAIDs. A clinical study conducted by Scheiman, et al. showed that, for at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs. Esomeprazole has advantages over misoprostol, which is also used to prevent ulcers in patients taking NSAIDs, including once daily dosing and decreased risk of adverse events. Vimovo represents an effective and convenient option to give one tablet for arthritis patients who must take NSAIDs to relieve their pain, but who are at risk of developing gastric ulcers.

REFERENCES

1. Vimovo™ [package insert]. Wilmington, DE: AstraZeneca LP; July 2010.
2. Clinical Pharmacology 2010. Vimovo™ monograph. [Accessed 2010 September]. Available from: <http://cpip.gsm.com/>.
3. Scheiman JM, Yeomans ND, Talley NJ, Vakil N, Chan FK, Tulassay Z, et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006 Apr; 101(4):701-10.