NAPROXEN AND ESOMEPRAZOLE MAGNESIUM tablet, film coated
Mylan Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NAPROXEN AND ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE TABLETS safely and effectively. See full prescribing information for NAPROXEN AND ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE TABLETS.

NAPROXEN and ESOMEPRAZOLE MAGNESIUM delayed-release tablets, for oral use
Initial U.S. Approval: 2010

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

- Non-steroidal 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)
- Naproxen and esomeprazole magnesium delayed-release tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)
- NSAIDs, including naproxen, a component of naproxen and esomeprazole magnesium delayed-release tablets, 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
Warnings and Precautions, Acute Tubulointerstitial Nephritis (5.18) 11/2020
Warnings and Precautions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (5.10) 4/2021
Warnings and Precautions, Fetal Toxicity (5.11) 4/2021

INDICATIONS AND USAGE
Naproxen and esomeprazole magnesium delayed-release tablets are 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets is indicated to decrease the risk of developing naproxen-associated gastric ulcers. (1)

Limitations of Use:
- Do not substitute naproxen and esomeprazole magnesium delayed-release tablets with the single-ingredient products of naproxen and esomeprazole magnesium. (1)
- Naproxen and esomeprazole magnesium delayed-release tablets are 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 naproxen and esomeprazole magnesium delayed-release 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 naproxen and esomeprazole magnesium delayed-release 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 naproxen and esomeprazole magnesium delayed-release 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

Naproxen and esomeprazole magnesium 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets 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: Naproxen and esomeprazole magnesium delayed-release tablets are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with pre-existing asthma (without aspirin sensitivity). (5.8)
- Serious Skin Reactions: Discontinue naproxen and esomeprazole magnesium delayed-release tablets at first appearance of skin rash or other signs of hypersensitivity. (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically. (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (5.11, 8.1)
• **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.12, 7)
• **Masking of Inflammation and Fever:** Potential for diminished utility of diagnostic signs in detecting infections. (5.13)
• **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. (5.14)
• **Active Bleeding:** Withdraw treatment in patients who experience active and clinically significant bleeding. (5.15)
• **Concomitant NSAID Use:** Do not use naproxen and esomeprazole magnesium delayed-release tablets with other naproxen-containing products or other non-aspirin NSAIDs. (5.16)
• **Gastric Malignancy:** In adults, symptomatic response to esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.17)
• **Acute Tubulointerstitial Nephritis:** Discontinue treatment and evaluate patients. (5.18)
• **Clostridium difficile-Associated Diarrhea:** PPI therapy may be associated with increased risk of *Clostridium difficile*-associated diarrhea. (5.19)
• **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. (5.20)
• **Cutaneous and Systemic Lupus Erythematosus:** Mostly cutaneous, new onset or exacerbation of existing disease; discontinue naproxen and esomeprazole magnesium delayed-release tablets and refer to specialist for evaluation. (5.21)
• **Interaction with Clopidogrel:** Avoid concomitant use. (5.22, 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. (5.23)
• **Hypomagnesemia:** Reported rarely with prolonged treatment with PPIs. (5.24)
• **Interaction with St. John’s Wort or Rifampin:** Avoid concomitant use. (5.25, 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. (5.26)
• **Interaction with Methotrexate:** Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. (5.27, 7)
• **Fundic Gland Polyps:** Risk increases with long-term PPI use, especially beyond one year. Use the shortest duration of therapy. (5.28)

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**ADVERSE REACTIONS**

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

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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**DRUG INTERACTIONS**

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

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**USE IN SPECIFIC POPULATIONS**

- **Females and Males of Reproductive Potential:** NSAIDs are associated with reversible infertility. Consider withdrawal of naproxen and esomeprazole magnesium delayed-release tablets in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 5/2021

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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 naproxen and esomeprazole magnesium delayed-release tablets, 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)].
- Naproxen and esomeprazole magnesium delayed-release tablets are 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 naproxen and esomeprazole magnesium delayed-release tablets 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

Naproxen and esomeprazole magnesium delayed-release tablets, a combination of naproxen and esomeprazole magnesium, are 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets is indicated to decrease the risk of developing naproxen-associated gastric ulcers.

Limitations of Use:

- Do not substitute naproxen and esomeprazole magnesium delayed-release tablets with the single-ingredient products of naproxen and esomeprazole magnesium.
- Naproxen and esomeprazole magnesium delayed-release tablets are 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 naproxen and esomeprazole magnesium delayed-release tablets and other treatment options before deciding to use naproxen and esomeprazole magnesium delayed-release tablets.
- Naproxen and esomeprazole magnesium delayed-release tablets do 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 naproxen and esomeprazole magnesium delayed-release tablets whole with liquid. Do not split, chew, crush or dissolve the tablet. Take naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets.

2.2 Recommended Dosage

The recommended dosage of naproxen and esomeprazole magnesium delayed-release tablets by indication is shown in the table:
<table>
<thead>
<tr>
<th>Indication</th>
<th>Patient Population</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis</td>
<td>Adults</td>
<td>One naproxen and esomeprazole magnesium delayed-release tablet twice daily of either: 375 mg naproxen/20 mg of esomeprazole; or 500 mg naproxen/20 mg of esomeprazole</td>
</tr>
<tr>
<td>Juvenile Idiopathic Arthritis in Adolescent Patients 12 Years of Age and Weighing at Least 38 kg</td>
<td>Greater than 50 kg</td>
<td>One naproxen and esomeprazole magnesium delayed-release tablet twice daily of: 375 mg naproxen/20 mg of esomeprazole</td>
</tr>
<tr>
<td></td>
<td>38 kg to less than 50 kg</td>
<td></td>
</tr>
</tbody>
</table>

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 naproxen and esomeprazole magnesium delayed-release tablets.

Naproxen and esomeprazole magnesium delayed-release tablets 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

Naproxen and Esomeprazole Magnesium Delayed-Release Tablets are available containing 375 mg or 500 mg of naproxen, USP and 22.25 mg of esomeprazole magnesium, USP equivalent to 20 mg of esomeprazole providing for the following combinations: 375 mg/20 mg and 500 mg/20 mg.

- The 375 mg/20 mg tablets are yellow, film-coated, oval, unscored tablets imprinted with NE1 in black ink on one side of the tablet and blank on the other side.
- The 500 mg/20 mg tablets are yellow, film-coated, oval, unscored tablets imprinted with NE2 in black ink on one side of the tablet and blank on the other side.

4 CONTRAINDICATIONS

Naproxen and esomeprazole magnesium delayed-release tablets are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to
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 naproxen and esomeprazole magnesium delayed-release tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If naproxen and esomeprazole magnesium delayed-release tablets are 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 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.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue naproxen and esomeprazole magnesium delayed-release tablets until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].
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.

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of the normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, and sometimes fatal, cases of severe hepatic injury, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including naproxen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue naproxen and esomeprazole magnesium delayed-release tablets immediately, and perform a clinical evaluation of the patient.

Naproxen and esomeprazole magnesium delayed-release tablets should be avoided in patients with severe hepatic impairment [see Dosage and Administration (2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].

5.4 Hypertension

NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazides diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

Avoid the use of naproxen and esomeprazole magnesium delayed-release tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If naproxen and esomeprazole magnesium delayed-release
tablets are used in patients with severe heart failure, monitor patients for signs and symptoms of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

**Renal Toxicity**

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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy was usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of naproxen and esomeprazole magnesium delayed-release tablets in patients with advanced renal disease. The renal effects of naproxen and esomeprazole magnesium delayed-release tablets may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating naproxen and esomeprazole magnesium delayed-release tablets. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of naproxen and esomeprazole magnesium delayed-release tablets [see Drug Interactions (7)]. Avoid the use of naproxen and esomeprazole magnesium delayed-release tablets in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal failure. If naproxen and esomeprazole magnesium delayed-release tablets are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

**Hyperkalemia**

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Naproxen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to naproxen and in patients with aspirin-sensitive asthma [see Contraindications (4) and Warnings and Precautions (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-
reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, naproxen and esomeprazole magnesium delayed-release tablets are contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When naproxen and esomeprazole magnesium delayed-release tablets are used in patients with pre-existing asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
NSAIDs, including naproxen, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of naproxen and esomeprazole magnesium delayed-release tablets at the first appearance of skin rash or any other sign of hypersensitivity. Naproxen and esomeprazole magnesium delayed-release tablets are contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as naproxen and esomeprazole magnesium delayed-release tablets. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue naproxen and esomeprazole magnesium delayed-release tablets and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus
Avoid use of NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, in pregnant women at about 30 weeks gestation and later. NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of
impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit naproxen and esomeprazole magnesium delayed-release tablet use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if naproxen and esomeprazole magnesium delayed-release tablet treatment is needed in a pregnant woman. Discontinue naproxen and esomeprazole magnesium delayed-release tablets if oligohydramnios occurs and follow up according to clinical practice [see Use in Specific Populations (8.1)].

5.12 Hematologic Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with naproxen and esomeprazole magnesium delayed-release tablets has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin and other anticoagulants, antiplatelet agents (e.g., aspirin), and serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase the risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

5.13 Masking of Inflammation and Fever
The pharmacological activity of naproxen and esomeprazole magnesium delayed-release tablets in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

5.15 Active Bleeding
When active and clinically significant bleeding from any source occurs in patients receiving naproxen and esomeprazole magnesium delayed-release tablets, the treatment should be withdrawn.

5.16 Concomitant NSAID Use
Naproxen and esomeprazole magnesium delayed-release tablets contain naproxen as one of their active ingredients. They should not be used with other naproxen-containing products since they all circulate in the plasma as the naproxen anion.

The concomitant use of naproxen and esomeprazole magnesium delayed-release tablets with any dose of a non-aspirin NSAID should be avoided due to the potential for
increased risk of adverse reactions.

5.17 Presence of Gastric Malignancy

In adults, response to gastric symptoms with naproxen and esomeprazole magnesium delayed-release tablets does not preclude the presence of gastric malignancy. Consider additional gastrointestinal follow-up and diagnostic testing in adult patients who experience gastric symptoms during treatment with naproxen and esomeprazole magnesium delayed-release tablets or have a symptomatic relapse after completing treatment. In older patients, also consider an endoscopy.

5.18 Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia).

Discontinue naproxen and esomeprazole magnesium delayed-release tablets and evaluate patients with suspected acute TIN [see Contraindications (4)].

5.19 Clostridium difficile-Associated Diarrhea

Published observational studies suggest that proton pump inhibitor (PPI) therapy like naproxen and esomeprazole magnesium delayed-release tablets may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated [see Dosage and Administration (2)].

5.20 Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines [see Dosage and Administration (2), Adverse Reactions (6.2)].

Naproxen and esomeprazole magnesium delayed-release tablets (a combination PPI/NSAID) are approved for use twice a day and do not allow for administration of a lower daily dose of the PPI [see Dosage and Administration (2)].

5.21 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including esomeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The
The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

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 naproxen and esomeprazole magnesium delayed-release tablets, 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.

5.22 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 naproxen and esomeprazole magnesium delayed-release tablets, consider alternative anti-platelet therapy [see Drug Interactions (7), Clinical Pharmacology (12.3)].

5.23 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.

5.24 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)].
5.25 Concomitant Use of St. John’s Wort or Rifampin with Naproxen and Esomeprazole Magnesium Delayed-Release Tablets

Drugs that induce CYP2C19 or CYP3A4 (such as St. John’s Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of naproxen and esomeprazole magnesium delayed-release tablets with St. John’s Wort or rifampin [see Drug Interactions (7)].

5.26 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)].

5.27 Concomitant Use of Naproxen and Esomeprazole Magnesium Delayed-Release Tablets with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [see Drug Interactions (7)].

5.28 Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [see Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration and Perforations [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.6)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.9)]
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.10)]
- Fetal Toxicity [see Warnings and Precautions (5.11)]
- Hematologic Toxicity [see Warnings and Precautions (5.12)]
Active Bleeding [see Warnings and Precautions (5.15)]
Acute Tubulointerstitial Nephritis [see Warnings and Precautions (5.18)]
Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.19)]
Bone Fracture [see Warnings and Precautions (5.20)]
Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.21)]
Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (5.23)]
Hypomagnesemia [see Warnings and Precautions (5.24)]
Fundic Gland Polyps [see Warnings and Precautions (5.28)]

6.1 Clinical Trials Experience

Clinical Trials Experience with Naproxen and Esomeprazole Magnesium Delayed-Release Tablets

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions reported below are specific to the clinical trials with naproxen and esomeprazole magnesium delayed-release tablets.

The safety of naproxen and esomeprazole magnesium delayed-release tablets was evaluated in clinical studies involving 2317 patients (aged 27 to 90 years) and ranging from 3 to 12 months. Patients received either 500 mg/20 mg of naproxen and esomeprazole magnesium delayed-release tablets twice daily (n = 1157), 500 mg of enteric-coated naproxen twice daily (n = 426), or placebo (n = 246). The average number of naproxen and esomeprazole magnesium delayed-release tablet doses taken over 12 months was 696 ± 44.

The table below lists all adverse reactions, regardless of causality, occurring in > 2% of patients receiving naproxen and esomeprazole magnesium delayed-release tablets and higher in the naproxen and esomeprazole magnesium delayed-release tablets group than control from two clinical studies (Study 1 and Study 2). Both of these studies were randomized, multi-center, double-blind, parallel studies. The majority of patients were female (67%), white (86%). The majority of patients were 50-69 years of age (83%).

Table 1: Adverse Reactions* in Study 1 and Study 2 (Endoscopic Studies)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Naproxen and Esomeprazole Magnesium Delayed-Release Tablets 500 mg/20 mg Twice Daily (n = 428)</th>
<th>EC-Naproxen 500 mg Twice Daily (n = 426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
In Study 1 and Study 2, patients taking naproxen and esomeprazole magnesium delayed-release tablets had fewer premature discontinuations due to adverse reactions compared to patients taking enteric-coated naproxen alone (7.9% vs 12.5% respectively). The most common reasons for discontinuations due to adverse events in the naproxen and esomeprazole magnesium delayed-release tablets treatment group were upper abdominal pain (1.2%, n = 5), duodenal ulcer (0.7%, n = 3) and erosive gastritis (0.7%, n = 3). Among patients receiving enteric-coated naproxen, the most common reasons for discontinuations due to adverse events were duodenal ulcer 5.4% (n = 23), dyspepsia 2.8% (n = 12) and upper abdominal pain 1.2% (n = 5). The proportion of patients discontinuing treatment due to any upper gastrointestinal adverse events (including duodenal ulcers) in patients treated with naproxen and esomeprazole magnesium delayed-release tablets was 4% compared to 12% for patients taking enteric-coated naproxen.

The table below lists all adverse reactions, regardless of causality, occurring in > 2% of patients and higher in the naproxen and esomeprazole magnesium delayed-release tablets group than placebo from 2 clinical studies conducted in patients with osteoarthritis of the knee (Study 3 and Study 4).

**Table 2: Adverse Reactions* in Study 3 and Study 4**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Naproxen and Esomeprazole Magnesium Delayed-Release Tablets 500 mg/20 mg Twice Daily (n = 490) %</th>
<th>Placebo (n = 246) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

* Reported in > 2% of patients and higher in the naproxen and esomeprazole magnesium delayed-release tablets group than placebo

The percentage of subjects who withdrew from the naproxen and esomeprazole magnesium delayed-release tablets treatment group in these studies due to treatment-emergent adverse events was 7%. There were no preferred terms in which more than 1% of subjects withdrew from any treatment group.

The long-term safety of naproxen and esomeprazole magnesium delayed-release tablets was evaluated in an open-label clinical trial of 239 patients, of which 135 patients received 500 mg/20 mg of naproxen and esomeprazole magnesium delayed-release tablets for 12 months. There were no differences in frequency or types of adverse reactions seen in the long-term safety study compared to shorter-term treatment in the
Clinical Trials Experience with Naproxen and Other NSAIDs

In patients taking naproxen in clinical trials, the most frequent reported adverse experiences in approximately 1% to 10% of patients are:

**Gastrointestinal:** heartburn, nausea, dyspepsia, stomatitis

**Central Nervous System:** drowsiness, lightheadedness, vertigo

**Dermatologic:** pruritus, skin eruptions, ecchymoses, sweating, purpura

**Special Senses:** tinnitus, visual disturbances, hearing disturbances

**Cardiovascular:** palpitations

**General:** dyspnea, thirst

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients:

**Gastrointestinal:** gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

**General:** abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in < 1% of patients taking naproxen during clinical trials:

**Gastrointestinal:** pancreatitis

**Hepatobiliary:** jaundice

**Hemic and Lymphatic:** melena, thrombocytopenia, agranulocytosis

**Nervous System:** inability to concentrate

**Dermatologic:** skin rashes

In patients taking NSAIDs, the following adverse experiences have also been reported in < 1% of patients:

**Body as a Whole:** fever, infection, sepsis, anaphylactic reactions, appetite changes, death

**Cardiovascular:** hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

**Gastrointestinal:** dry mouth, glossitis, eructation

**Hepatobiliary:** hepatitis, liver failure

**Hemic and Lymphatic:** rectal bleeding, lymphadenopathy, pancytopenia

**Metabolic and Nutritional:** weight changes

**Nervous System:** anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremor, coma, hallucinations

**Respiratory:** asthma, respiratory depression, pneumonia
**Dermatologic:** exfoliative dermatitis

**Special Senses:** blurred vision, conjunctivitis

**Urogenital:** cystitis, dysuria, oliguria/polyuria, proteinuria

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**Clinical Trials Experience with Esomeprazole Magnesium**

Additional adverse reactions that were reported as possibly or probably related to esomeprazole magnesium with an incidence of < 1% are listed below by body system:

**Body as a Whole:** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, malaise, pain, rigors

**Cardiovascular:** flushing, hypertension, tachycardia

**Endocrine:** goiter

**Gastrointestinal:** dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccups, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting

**Hearing:** earache, tinnitus

**Hematologic:** anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia

**Hepatic:** bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased

**Metabolic/Nutritional:** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B-12 deficiency, weight increase, weight decrease

**Musculoskeletal:** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica

**Nervous System/Psychiatric:** anorexia, apathy, appetite increased, confusion, depression aggravated, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect

**Reproductive:** dysmenorrhea, menstrual disorder, vaginitis

**Respiratory:** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis

**Skin and Appendages:** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria

**Special Senses:** otorhinology, parosmia, taste loss

**Urogenital:** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria

**Visual:** conjunctivitis, vision abnormal

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole magnesium, were reported in ≤ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST,
hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone.

Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

Endoscopic findings that were reported as adverse reactions include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, hernia, benign polyps or nodules, Barrett’s esophagus, and mucosal discoloration.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of naproxen and esomeprazole magnesium delayed-release tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Naproxen and Esomeprazole Magnesium Delayed-Release Tablets**

*Body as a Whole*: gait disturbance

*Gastrointestinal*: abdominal distension, abdominal pain, gastroesophageal reflux, hematochezia

*Injury, Poisoning and Procedural Complications*: contusion, fall

*Musculoskeletal and Connective Tissue*: joint swelling, muscle spasms

*Urogenital*: renal tubular necrosis

**Naproxen**

*Body as a Whole*: angioneurotic edema, menstrual disorders

*Cardiovascular*: congestive heart failure, vasculitis, pulmonary edema

*Gastrointestinal*: inflammation, bleeding (sometimes fatal, particularly in the elderly), ulceration, and obstruction of the upper or lower gastrointestinal tract, esophagitis, stomatitis, hematemesis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn’s disease)

*Hepatobiliary*: hepatitis (some cases have been fatal)

*Hemic and Lymphatic*: eosinophilia, hemolytic anemia, aplastic anemia

*Metabolic and Nutritional*: hyperglycemia, hypoglycemia

*Nervous System*: depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions

*Respiratory*: eosinophilic pneumonitis

*Dermatologic*: alopecia, urticaria, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematosus, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other
symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Special Senses: hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema

Urogenital: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine

Reproduction (female): infertility

Esomeprazole Magnesium

Blood and Lymphatic: agranulocytosis

Eye: blurred vision

Gastrointestinal: pancreatitis, microscopic colitis, fundic gland polyps

Hepatobiliary: hepatic failure, hepatitis with or without jaundice

Immune System: anaphylactic reaction/shock, systemic lupus erythematosus

Infections and Infestations: GI candidiasis, *Clostridium difficile*-associated diarrhea

Metabolism and Nutritional Disorders: hypomagnesemia, with or without hypocalcemia and/or hypokalemia

Musculoskeletal and Connective Tissue: muscular weakness, myalgia, bone fracture

Nervous System: hepatic encephalopathy

Psychiatric: aggression, agitation, hallucination

Renal and Urinary: interstitial nephritis

Reproductive System and Breast: gynecomastia

Respiratory, Thoracic, and Mediastinal: bronchospasm

Skin and Subcutaneous Tissue: alopecia, erythema multiforme, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal), cutaneous lupus erythematosus

7 DRUG INTERACTIONS

See Table 3 and Table 4 for clinically significant drug interactions and interactions with diagnostics with naproxen and esomeprazole magnesium.

<table>
<thead>
<tr>
<th>Drugs That Interfere with Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen:</td>
</tr>
<tr>
<td>• Naproxen and anticoagulants such as warfarin have a</td>
</tr>
</tbody>
</table>
Clinical Impact:

**Esomeprazole Magnesium:**
- Increased INR and prothrombin time in patients treated with PPIs, including esomeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
- Concomitant use of esomeprazole 40 mg resulted in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition [see Clinical Pharmacology (12.3)].
- There are no adequate combination studies of a lower dose of esomeprazole or a higher dose of clopidogrel in comparison with the approved dose of clopidogrel.

**Intervention:** [see Warnings and Precautions (5.14)].

**Clopidogrel:** Avoid concomitant use of clopidogrel with naproxen and esomeprazole magnesium delayed-release tablets. Consider use of alternative anti-platelet therapy [see Warnings and Precautions (5.22)].

**Aspirin**

A pharmacodynamics (PD) study has demonstrated an interaction in which lower dose naproxen (220 mg/day or 220 mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen [see Clinical Pharmacology (12.2)]. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the PD study due to the longer washout period.

**Clinical Impact:**

Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as
compared to use of the NSAID alone [see Warnings and Precautions (5.2)].

Because there may be an increased risk of cardiovascular events following discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics where appropriate.

**Intervention:**
Concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see Warnings and Precautions (5.12)].

Naproxen and esomeprazole magnesium delayed-release tablets are not a substitute for low-dose aspirin for cardiovascular protection.

### ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers

**Clinical Impact:**
- NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

**Intervention:**
- During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.
- During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and ACE inhibitors or ARBs in patients who are elderly, volume-depleted or have impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)].

### Diuretics

**Clinical Impact:**
Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.

**Intervention:**
During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets with diuretics, observe patients for signs of worsening renal function, in addition to assuring
<table>
<thead>
<tr>
<th><strong>Antiretrovirals</strong></th>
<th>The effect of esomeprazole magnesium on antiretroviral drugs is variable. The clinical importance and mechanisms behind these interactions are not always known.</th>
</tr>
</thead>
</table>
| **Clinical Impact:** | - Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with esomeprazole magnesium may reduce antiviral effect and promote the development of drug resistance [see Clinical Pharmacology (12.3)].  
- Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with esomeprazole magnesium may increase toxicity [see Clinical Pharmacology (12.3)].  
- There are other antiretroviral drugs which do not result in clinically relevant interactions with esomeprazole magnesium. |
| **Intervention:** | Rilpivirine-containing Products: Concomitant use with naproxen and esomeprazole magnesium delayed-release tablets is contraindicated [see Contraindications (4)].  
Atazanavir: See prescribing information for atazanavir for dosing information.  
Nelfinavir: Avoid concomitant use with naproxen and esomeprazole magnesium delayed-release tablets.  
Saquinavir: See the prescribing information for saquinavir for monitoring of potential saquinavir-related toxicities.  
Other Antiretrovirals: See prescribing information of specific drugs. |
| **Cilostazol** | Increased exposure of cilostazol and one of its active metabolites (3,4-dihydro-cilostazol) when co-administered with omeprazole magnesium, the racemate of esomeprazole [see Clinical Pharmacology (12.3)]. |
| **Clinical Impact:** |  |
| **Intervention:** | Consider reducing the dose of cilostazol to 50 mg twice daily. |
| **Digoxin** | Naproxen:  
- The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. |
| **Clinical Impact:** | Esomeprazole Magnesium:  
- Potential for increased exposure of digoxin [see Clinical Pharmacology (12.3)]. |
<p>| <strong>Intervention:</strong> | Monitor digoxin concentrations during concomitant use of naproxen and esomeprazole magnesium delayed-release tablets. Dose adjustment of digoxin may be needed to maintain therapeutic... |</p>
<table>
<thead>
<tr>
<th><strong>Lithium</strong></th>
<th><strong>Clinical Impact:</strong> NSAIDs have produced elevations of plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and lithium, monitor patients for signs of lithium toxicity.</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Methotrexate</strong></th>
<th><strong>Naproxen:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact:</strong> Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).</td>
<td></td>
</tr>
<tr>
<td><strong>Esomeprazole Magnesium:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Impact:</strong> Concomitant use of esomeprazole magnesium with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities [see Warnings and Precautions (5.27)].</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention:</strong> During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and methotrexate, monitor patients for methotrexate toxicity. A temporary withdrawal of naproxen and esomeprazole magnesium delayed-release tablets may be considered in some patients receiving high-dose methotrexate.</td>
<td></td>
</tr>
</tbody>
</table>

| **Cyclosporine** | **Clinical Impact:** Concomitant use of naproxen and cyclosporine may increase cyclosporine’s nephrotoxicity. |
| **Intervention:** During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and cyclosporine, monitor patients for signs of worsening renal function. |

| **Tacrolimus** | **Clinical Impact:** Concomitant use of esomeprazole magnesium and tacrolimus may increase exposure of tacrolimus. |
| **Intervention:** During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and tacrolimus, monitor tacrolimus whole blood concentrations. |

| **NSAIDs and Salicylates** | **Clinical Impact:** Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)]. |
| **Intervention:** The concomitant use of naproxen and esomeprazole magnesium delayed-release tablets with other NSAIDs or salicylates is not |
### Pemetrexed

**Clinical Impact:** Concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).

**Intervention:** During concomitant use of naproxen and esomeprazole magnesium delayed-release tablets and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.

### Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, mycophenolate mofetil, ketoconazole)

**Clinical Impact:** Esomeprazole magnesium can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

**Intervention:** Mycophenolate Mofetil (MMF): Co-administration of omeprazole, of which esomeprazole magnesium is an enantiomer, in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use naproxen and esomeprazole magnesium delayed-release tablets with caution in transplant patients receiving MMF [see Clinical Pharmacology (12.3)].

See the prescribing information for other drugs dependent on gastric pH for absorption.

### Interactions with Investigations of Neuroendocrine Tumors

**Clinical Impact:** Serum chromogranin A (CgA) levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors [see Warnings and Precautions (5.25), Clinical Pharmacology (12.2)].

**Intervention:** Temporarily stop naproxen and esomeprazole magnesium delayed-release tablet 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.

### Diazepam

**Clinical Impact:** Increased exposure of diazepam [see Clinical Pharmacology (12.3)].

**Intervention:** Monitor patients for increased sedation and adjust the dose of diazepam as needed.

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### Table 4: Clinically Significant Interactions with Esomeprazole Magnesium --
Affecting Co-Administered Drugs

<table>
<thead>
<tr>
<th>CYP2C19 or CYP3A4 Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact:</strong></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
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</table>

<table>
<thead>
<tr>
<th>CYP2C19 or CYP3A4 Inhibitors</th>
</tr>
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<tbody>
<tr>
<td><strong>Clinical Impact:</strong></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, can cause premature closure of the fetal ductus arteriosus and fetal and renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of naproxen and esomeprazole magnesium delayed-release tablet use between about 20 and 30 weeks of gestation and avoid naproxen and esomeprazole magnesium delayed-release tablet use at about 30 weeks of gestation and later in pregnancy (see Clinical Considerations, Data).

Premature Closure of the Fetal Ductus Arteriosus

Use of NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Naproxen and esomeprazole magnesium delayed-release tablets contain naproxen and esomeprazole magnesium. Esomeprazole is the S-isomer of omeprazole.

Naproxen

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, naproxen administered during organogenesis to rats and rabbits at doses less than the maximum recommended human daily dose of 1500 mg/day showed no evidence of harm to the fetus (see Data). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular
permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen resulted in increased pre- and post-implantation loss.

Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

**Esomeprazole**

There are no human data for esomeprazole. However, available epidemiologic data for omeprazole (esomeprazole is the S-isomer of omeprazole) fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use (see Data). In animal studies with administration of oral esomeprazole magnesium in rats, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age (see Data).

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Clinical Considerations**

**Fetal/Neonatal Adverse Reactions**

**Premature Closure of Fetal Ductus Arteriosus**

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, can cause premature closure of the fetal ductus arteriosus (see Data).

**Oligohydramnios/Neonatal Renal Impairment**

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If naproxen and esomeprazole magnesium delayed-release tablet treatment is needed in pregnant women, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue naproxen and esomeprazole magnesium delayed-release tablets and follow up according to clinical practice (see Data).

**Labor or Delivery**

There are no studies on the effects of naproxen and esomeprazole magnesium delayed-release tablets during labor or delivery. In animal studies, NSAIDs, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.
**Data**

**Human Data**

**Naproxen**

When used to delay preterm labor, inhibitors of prostaglandin synthesis, including NSAIDs such as naproxen, may increase the risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants.

Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

**Esomeprazole**

Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H₂-receptor antagonists or other controls.

A population-based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995-99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed in utero to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the
omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996-2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837,317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H₂-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H₂-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease-paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Animal Data

There are no reproduction studies in animals with naproxen and esomeprazole magnesium delayed-release tablets, a combination of naproxen and esomeprazole.

Naproxen

Reproduction studies with naproxen administered during the period of organogenesis have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison), rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose based on body surface area comparison), and mice at 170 mg/kg/day (0.56 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of harm to the fetus due to the drug.

Esomeprazole

No effects on embryo-fetal development were observed in reproduction studies with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) or in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg esomeprazole or 40 mg omeprazole on a body surface area basis) administered during organogenesis and have revealed no evidence of harm to the fetus due to esomeprazole magnesium.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development were performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times a daily human dose of 40 mg on a
body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times a daily human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times the daily human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in the pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above. A follow up developmental toxicity study in rats with further time points to evaluate pup bone development from postnatal day 2 to adulthood was performed with esomeprazole magnesium at oral doses of 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) where esomeprazole administration was from either gestational day 7 or gestational day 16 until parturition. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

8.2 Lactation

Risk Summary

Limited data from published literature report that naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Esomeprazole is the S-isomer of omeprazole and limited data from published literature suggest omeprazole may be present in human milk. There is no information on the effects of naproxen or omeprazole on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for naproxen and esomeprazole magnesium delayed-release tablets and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility
Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, may delay or prevent rupture of ovarian follicles that may lead to reversible infertility in some women. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Published animal studies have shown that administration of prostaglandin synthesis inhibitors have the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Consider withdrawal of NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

The safety and effectiveness of naproxen and esomeprazole magnesium delayed-release tablets have been established in adolescent patients 12 years of age and older weighing at least 38 kg for the symptomatic relief of JIA and to decrease the risk of developing naproxen-associated gastric ulcers. Use of naproxen and esomeprazole magnesium delayed-release tablets in this age group is based on extrapolation of adequate and well-controlled studies in adults and supported by a 6-month safety study including pharmacokinetic assessment of naproxen and esomeprazole magnesium in 36 adolescent patients with JIA. Based on the limited data, the plasma naproxen and plasma esomeprazole concentrations were found to be within the range to that observed to those found in healthy adults. The safety profile of naproxen and esomeprazole magnesium delayed-release tablets in adolescent patients with JIA was similar to adults with RA.

The safety and effectiveness of naproxen and esomeprazole magnesium delayed-release tablets in pediatric patients less than 12 years of age or less than 38 kg with JIA have not been established.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)].

Of the total number of patients who received naproxen and esomeprazole magnesium delayed-release tablets (n = 1157) in clinical trials, 387 were ≥ 65 years of age, of which 85 patients were 75 years and over. No meaningful differences in efficacy or safety were observed between these subjects and younger subjects [see Adverse Reactions (6)].
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose [see Dosage and Administration (2), Clinical Pharmacology (12.3)].

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of NSAIDs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population [see Warnings and Precautions (5.2)].

Naproxen and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of NSAIDs [see Warnings and Precautions (5.6)].

8.6 Hepatic Impairment

Naproxen and esomeprazole magnesium delayed-release tablets should be avoided in patients with severe hepatic impairment because naproxen may increase the risk of renal failure or bleeding and esomeprazole doses should not exceed 20 mg daily in these patients [see Dosage and Administration (2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

8.7 Renal Impairment

Naproxen-containing products, including naproxen and esomeprazole magnesium delayed-release tablets, are not recommended for use in patients with advanced renal disease [see Dosage and Administration (2), Warnings and Precautions (5.6)].

10 OVERDOSAGE

There is no clinical data on overdosage with naproxen and esomeprazole magnesium delayed-release tablets.

Overdosage of Naproxen: Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred but were rare [see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)].

A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life-threatening. The oral LD50 of the drug is 500 mg/kg in rats, 1200 mg/kg in mice, 4000 mg/kg in hamsters and greater than 1000 mg/kg in dogs. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Consider
emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

**Overdosage of Esomeprazole:** A single oral dose of esomeprazole at 510 mg/kg (about 124 times the human dose on a body surface area basis) was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - Adverse Reactions). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

**11 DESCRIPTION**

The active ingredients of naproxen and esomeprazole magnesium delayed-release tablets are naproxen which is an NSAID and esomeprazole magnesium which is a Proton Pump Inhibitor (PPI).

Naproxen and esomeprazole magnesium delayed-release tablets are a combination of a non-steroidal anti-inflammatory drug and a PPI available as an oval, yellow, film-coated, multi-layer, delayed-release tablet combining an enteric-coated naproxen core and an immediate-release esomeprazole magnesium layer surrounding the core.

Each strength contains either 375 mg of naproxen and 20 mg of esomeprazole (equivalent to 22.25 mg esomeprazole magnesium) or 500 mg of naproxen and 20 mg of esomeprazole (equivalent to 22.25 mg esomeprazole magnesium) for oral administration. The inactive ingredients are acetylated monoglycerides, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, mono and diglycerides, polyethylene glycol, polysorbate 80, povidone, propylene glycol, sodium carbonate anhydrous, titanium dioxide, triethyl citrate and yellow iron oxide. The black imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol and shellac glaze.

The chemical name for naproxen is (S)-6-Methoxy-α-methyl-2-naphthalene acetic acid. Naproxen has the following structure:
Naproxen has a molecular weight of 230.26 and a molecular formula of C\textsubscript{14}H\textsubscript{14}O\textsubscript{3}.

Naproxen, USP is an odorless, white to almost white crystalline powder. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8.

The chemical name for esomeprazole is 5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl] benzimidazole, magnesium salt (2:1). Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. Its molecular formula is C\textsubscript{34}H\textsubscript{36}MgN\textsubscript{6}O\textsubscript{6}S\textsubscript{2} with molecular weight of 713.12 on an anhydrous basis. The structural formula is:

\[\text{\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{Structural formula of esomeprazole magnesium.}
\end{figure}}\]  

The magnesium salt is an off-white to pale cream colored powder. It is slightly soluble in water.

The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naproxen and esomeprazole magnesium delayed-release tablets consist of an immediate-release esomeprazole magnesium layer and an enteric-coated naproxen core. As a result, esomeprazole is released first in the stomach, prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5.5.

The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but inhibition of cyclooxygenase (COX-1 and COX-2).

Naproxen and esomeprazole magnesium delayed-release tablets have analgesic, anti-inflammatory, and antipyretic properties contributed by the naproxen component.
Naproxen is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to an increase of prostaglandins in peripheral tissues.

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. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

### 12.2 Pharmacodynamics

**Interaction with Aspirin**

In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once-daily with low-dose immediate-release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B\(_2\) inhibition at 24 hours following the day 10 dose [98.7% (aspirin alone) vs 93.1% (naproxen and aspirin)]. The interaction was observed even following discontinuation of naproxen on day 11 (while aspirin dose was continued) but normalized by day 13. In the same study, the interaction was greater when naproxen was administered 30 minutes prior to aspirin [98.7% vs 87.7%] and minimal when aspirin was administered 30 minutes prior to naproxen [98.7% vs 95.4%].

Following administration of naproxen 220 mg twice-daily with low-dose immediate-release aspirin (first naproxen dose given 30 minutes prior to aspirin), the interaction was minimal at 24 h following day 10 dose [98.7% vs 95.7%]. However, the interaction was more prominent after discontinuation of naproxen (washout) on day 11 [98.7% vs 84.3%] and did not normalize completely by day 13 [98.5% vs 90.7%] [see Drug Interactions (7)].

**Antisecretory Activity**

The effect of naproxen and esomeprazole magnesium delayed-release tablets on intragastric pH was determined in 25 healthy volunteers in one study. Three naproxen and esomeprazole magnesium delayed-release tablet combinations (naproxen 500 mg combined with either esomeprazole 10, 20, or 30 mg) were administered twice daily over 9 days. The results are shown in the following table:

<table>
<thead>
<tr>
<th>% Time Gastric pH &gt; 4*</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean (SE)</td>
<td>41.1 (3.0)</td>
<td>71.5 (3.0)</td>
<td>76.8 (3.0)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>55%</td>
<td>18%</td>
<td>16%</td>
</tr>
</tbody>
</table>

**Table 5: Effect on Intragastric pH on Day 9 (N = 25)**
Serum Gastrin Effects

The effect of esomeprazole on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare 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.

Enterochromaffin-like (ECL) Cell Effects

In over 1,000 patients treated with esomeprazole (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

Esomeprazole had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of esomeprazole on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

Effects on Gastrointestinal Microbial Ecology

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalized patients, possibly also Clostridium difficile.

12.3 Pharmacokinetics

Absorption

Naproxen

At steady state following administration of naproxen and esomeprazole magnesium delayed-release tablets twice daily, peak plasma concentrations of naproxen are reached on average 3 hours following both the morning and the evening dose.

Bioequivalence between naproxen and esomeprazole magnesium delayed-release tablets and enteric-coated naproxen, based on both area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_max) of naproxen, has been demonstrated for both the 375 mg and 500 mg doses.
Naproxen is absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. Steady-state levels of naproxen are reached in 4 to 5 days.

**Esomeprazole**

Following administration of naproxen and esomeprazole magnesium delayed-release tablets twice daily, esomeprazole is rapidly absorbed with peak plasma concentration reached within on average, 0.43 to 1.2 hours, following the morning and evening dose on both the first day of administration and at steady state. The peak plasma concentrations of esomeprazole are higher at steady state compared to on first day of dosing of naproxen and esomeprazole magnesium delayed-release tablets.

Figure 1 represents the pharmacokinetics of naproxen and esomeprazole following administration of naproxen and esomeprazole magnesium delayed-release tablets 500 mg/20 mg.

![Graph](image)

**Figure 1: Mean Plasma Concentrations of Naproxen and Esomeprazole Following Single Dose Administration of Naproxen and Esomeprazole Magnesium Delayed-Release Tablets (500 mg/20 mg)**

**Food Effect**

Administration of naproxen and esomeprazole magnesium delayed-release tablets together with high-fat food in healthy volunteers does not affect the extent of absorption of naproxen but significantly prolongs $t_{\text{max}}$ by 10 hours and decreases peak plasma concentration ($C_{\text{max}}$) by about 12%.

Administration of naproxen and esomeprazole magnesium delayed-release tablets together with high-fat food in healthy volunteers delays $t_{\text{max}}$ of esomeprazole by 1 hour and significantly reduces the extent of absorption, resulting in 52% and 75% reductions.
of area under the plasma concentration versus time curve (AUC) and peak plasma concentration (C_{max}), respectively.

Administration of naproxen and esomeprazole magnesium delayed-release tablets 30 minutes before high-fat food intake in healthy volunteers does not affect the extent of absorption of naproxen but delays the absorption by about 4 hours and decreases peak plasma concentration (C_{max}) by about 17%, but has no significant effect on the rate or extent of esomeprazole absorption compared to administration under fasted conditions [see Dosage and Administration (2)].

Administration of naproxen and esomeprazole magnesium delayed-release tablets 60 minutes before high-fat food intake in healthy volunteers has no effect on the rate and extent of naproxen absorption; however, increases the esomeprazole AUC by 25% and C_{max} by 50% compared to administration under fasted conditions. This increase in esomeprazole C_{max} does not raise a safety issue since the approved dosing regimen of esomeprazole at 40 mg QD would result in higher C_{max} [see Dosage and Administration (2)].

Therefore, naproxen and esomeprazole magnesium delayed-release tablets should be taken at least 30 minutes before the meal.

**Distribution**

**Naproxen**

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma [see Use in Specific Populations (8.2)].

**Esomeprazole**

The apparent volume of distribution at steady state in healthy subjects is approximately 16 L. Esomeprazole is 97% plasma protein bound.

**Elimination**

**Metabolism**

**Naproxen**

Naproxen is extensively metabolized in the liver by the cytochrome P450 system (CYP), CYP2C9 and CYP1A2, to 6-0-desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites. Consistent with the half-life of naproxen, the area under the plasma concentration time curve increases with repeated dosing of naproxen and esomeprazole magnesium delayed-release tablets twice daily.
Esomeprazole

Esomeprazole is extensively metabolized in the liver by the CYP enzyme system. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxyl- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma. The major metabolites of esomeprazole have no effect on gastric acid secretion.

The area under the plasma esomeprazole concentration-time curve increases with repeated administration of naproxen and esomeprazole magnesium delayed-release tablets. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. An increased absorption of esomeprazole with repeated administration of naproxen and esomeprazole magnesium delayed-release tablets probably also contributes to the time- and dose-dependency.

Excretion

Naproxen

Following administration of naproxen and esomeprazole magnesium delayed-release tablets twice daily, the mean elimination half-life for naproxen is approximately 15 hours following the evening dose, with no change with repeated dosing.

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (< 1%), 6-0-desmethyl naproxen (< 1%) or their conjugates (66% to 92%). Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure, metabolites may accumulate [see Warnings and Precautions (5.6)].

Esomeprazole

Following administration of naproxen and esomeprazole magnesium delayed-release tablets twice daily, the mean elimination half-life of esomeprazole is approximately 1 hour following both the morning and evening dose on day 1, with a slightly longer elimination half-life at steady state (1.2-1.5 hours).

Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the feces. Less than 1% of the parent drug is found in the urine.

Specific Populations

Geriatric Patients

There is no specific data on the pharmacokinetics of naproxen and esomeprazole magnesium delayed-release tablets in patients over age 65.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is < 1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The
clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients [see Adverse Reactions (6) and Use in Specific Populations (8.5)].

The AUC and C_max values of esomeprazole were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment for the esomeprazole component based on age is not necessary.

Male and Female Patients

The AUC and C_max values of esomeprazole were slightly higher (13%) in females than in males at steady state. Dosage adjustment for the esomeprazole component based on gender is not necessary.

Racial or Ethnic Groups

Pharmacokinetic differences due to race have not been studied for naproxen. Approximately 3% of Caucasians and 15 to 20% of Asians lack a functional CYP2C19 enzyme and are called poor metabolizers. In these individuals the metabolism of esomeprazole is probably mainly catalyzed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers).

Patients with Renal Impairment

The pharmacokinetics of naproxen and esomeprazole magnesium delayed-release tablets or naproxen have not been determined in subjects with renal impairment. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal impairment. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products, including naproxen and esomeprazole magnesium delayed-release tablets, are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance < 30 mL/min) [see Dosage and Administration (2), Warnings and Precautions (5.6), Use in Specific Populations (8.7)].

No studies have been performed with esomeprazole in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Patients with Hepatic Impairment

The pharmacokinetics of naproxen and esomeprazole magnesium delayed-release tablets or naproxen have not been determined in subjects with hepatic impairment. In patients with severe hepatic impairment, naproxen and esomeprazole magnesium delayed-release tablets should be avoided due to increase of risk of NSAID associated bleeding and/or renal failure associated with naproxen.

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the
The total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for the naproxen component of naproxen and esomeprazole magnesium delayed-release tablet dosing is unknown but it is prudent to use the lowest effective dose.

The AUCs of esomeprazole in patients with severe hepatic impairment (Child Pugh Class C) have been shown to be 2-3 times higher than in patients with normal liver function. For this reason, it has been recommended that esomeprazole doses not exceed 20 mg daily in patients with severe hepatic impairment. However, there is no dose adjustment necessary for patients with Child Pugh Class A and B for the esomeprazole component of naproxen and esomeprazole magnesium delayed-release tablets. There is no naproxen and esomeprazole magnesium delayed-release tablet dosage form that contains less than 20 mg esomeprazole for twice daily dosing [see Dosage and Administration (2), Warnings and Precautions (5.3)].

**Drug Interaction Studies**

*Effect of Naproxen on Other Drugs*

**Aspirin**

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [see Drug Interactions (7)].

*Effect of Esomeprazole on Other Drugs*

**Cytochrome P450 Interactions**

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin.

**Clopidogrel**

Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite [see Warnings and Precautions (5.22), Drug Interactions (7)].

**Mycophenolate Mofetil**
Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the $C_{\text{max}}$ and 23% reduction in the AUC of MPA [see Drug Interactions (7)].

**Cilostazol**

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased $C_{\text{max}}$ and AUC of cilostazol by 18% and 26%, respectively. $C_{\text{max}}$ and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69%, respectively [see Drug Interactions (7)].

**Nelfinavir**

Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg once a day), AUC was decreased by 36% and 92%, $C_{\text{max}}$ by 37% and 89% and $C_{\text{min}}$ by 39% and 75%, respectively for nelfinavir and main oxidative metabolite, hydroxy-t-butylamide (M8) [see Drug Interactions (7)].

**Atazanavir**

Following multiple doses of atazanavir (400 mg, once a day) and omeprazole (40 mg, once a day, 2 hr before atazanavir), AUC was decreased by 94%, $C_{\text{max}}$ by 96%, and $C_{\text{min}}$ by 95% [see Drug Interactions (7)].

**Saquinavir**

Elevated serum levels have been reported with an increase in AUC by 82%, in $C_{\text{max}}$ by 75% and in $C_{\text{min}}$ by 106% following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice a day for 15 days with omeprazole 40 mg once a day co-administered on days 11 to 15 [see Drug Interactions (7)].

**Diazepam**

Co-administration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam [see Drug Interactions (7)].

**Digoxin**

Concomitant administration of omeprazole 20 mg once daily and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects) [see Drug Interactions (7)].

*Effect of Other Drugs on Esomeprazole*

Because esomeprazole is metabolized by CYP2C19 and CYP3A4, inducers and inhibitors of these enzymes may potentially alter exposure of esomeprazole.

*St. John’s Wort*
In a cross-over study in 12 healthy male subjects, St. John’s Wort (300 mg three times
daily for 14 days) significantly decreased the systemic exposure of omeprazole in
CYP2C19 poor metabolizers (\(C_{\text{max}}\) and AUC decreased by 37.5% and 37.9%,
respectively) and extensive metabolizers (\(C_{\text{max}}\) and AUC decreased by 49.6% and
43.9%, respectively) [see Warnings and Precautions (5.25), Drug Interactions (7)].

**Voriconazole**

Concomitant administration of omeprazole and voriconazole (a combined inhibitor of
CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure.
When voriconazole (400 mg every 12 hours for one day, followed by 200 mg once daily
for 6 days) was given with omeprazole (40 mg once daily for 7 days) to healthy
subjects, the steady-state \(C_{\text{max}}\) and AUC\(_{0-24}\) of omeprazole significantly increased: an
average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as
compared to when omeprazole was given without voriconazole [see Drug Interactions
(7)].

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis**

**Naproxen**

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen
at rat doses of 8, 16, and 24 mg/kg/day (0.05, 0.1, and 0.16 times the maximum
recommended human daily dose of 1500 mg/day based on a body surface area
comparison). The maximum dose used was 0.28 times the highest recommended
human dose. No evidence of tumorigenicity was found.

**Esomeprazole**

The carcinogenic potential of esomeprazole was assessed using omeprazole studies, of
which esomeprazole is an enantiomer. In two 24-month oral carcinogenicity studies in
rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44 and 140.8 mg/kg/day (about 0.41
to 34.2 times the human dose of 40 mg/day expressed on a body surface area basis)
produced gastric ECL cell carcinoids in a dose-related manner in both male and female
rats; the incidence of this effect was markedly higher in female rats, which had higher
blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In
addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of
these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.36
times the human dose of 40 mg/day on a body surface area basis) for 1 year, then
followed for an additional year without the drug. No carcinoids were seen in these rats.
An increased incidence of treatment-related ECL cell hyperplasia was observed at the
end of 1 year (94% treated vs 10% controls). By the second year the difference
between treated and control rats was much smaller (46% vs 26%) but still showed more
hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No
similar tumor was seen in male or female rats treated for 2 years. For this strain of rat,
no similar tumor has been noted historically, but a finding involving only one tumor is
difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not
show increased tumor occurrence, but the study was not conclusive.

**Mutagenesis**

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow
cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome
aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome
aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and
the *in vivo* mouse micronucleus test.

**Impairment of Fertility**

The potential effects of esomeprazole on fertility and reproductive performance were
assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 33.6 times the human dose of 40 mg/day on a body surface area basis) was
found to have no effect on reproductive performance of parental animals.

Studies to evaluate the impact of naproxen on male or female fertility have not been
completed.

**13.2 Animal Toxicology and/or Pharmacology**

**Naproxen**

Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m²/day, 0.23 times the maximum recommended human dose), rabbits at 20 mg/kg/day (220 mg/m²/day, 0.27 times the maximum recommended human dose), and mice at 170 mg/kg/day (510 mg/m²/day, 0.28 times the maximum recommended human dose) with
no evidence of impaired fertility or harm to the fetus due to the drug. However, animal
reproduction studies are not always predictive of human response.

**Esomeprazole – Reproduction Studies**

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day
(about 68 times an oral human dose of 40 mg on a body surface area basis) and in
rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg
on a body surface area basis) and have revealed no evidence of impaired fertility or
harm to the fetus due to esomeprazole [see Use in Specific Populations (8.1)].

**Esomeprazole – Juvenile Animal Data**

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats
with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 68 times a
daily oral human dose of 40 mg on a body surface area basis). An increase in the
number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats
were administered esomeprazole magnesium from postnatal day 7 through postnatal
day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a
daily oral human dose of 40 mg on a body surface area basis), produced treatment-
related decreases in body weight (approximately 14%) and body weight gain, decreases
in femur weight and femur length, and affected overall growth. Comparable findings
described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

Two randomized, multi-center, double-blind trials (Study 1 and Study 2) compared the incidence of gastric ulcer formation in 428 patients taking naproxen and esomeprazole magnesium delayed-release tablets and 426 patients taking enteric-coated naproxen. Subjects were at least 18 years of age with a medical condition expected to require daily NSAID therapy for at least 6 months, and, if less than 50 years old, with a documented history of gastric or duodenal ulcer within the past 5 years. The majority of patients were female (67%), white (86%). The majority of patients were 50-69 years of age (83%).

Studies 1 and 2 showed that naproxen and esomeprazole magnesium delayed-release tablets given as 500 mg/20 mg twice daily statistically significantly reduced the 6-month cumulative incidence of gastric ulcers compared to enteric-coated naproxen 500 mg twice daily (see Table 6).

The results at 1 month, 3 months, and 6 months are presented in Table 6.

Table 6: Cumulative Observed Incidence of Gastric Ulcers at 1, 3 and 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naproxen and Esomeprazole Magnesium Delayed-Release Tablets N = 218 number (%)</td>
<td>EC-naproxen N = 216 number (%)</td>
</tr>
<tr>
<td>0-1 Month</td>
<td>3 (1.4)</td>
<td>28 (13.0)</td>
</tr>
<tr>
<td>0-3 Months</td>
<td>4 (1.8)</td>
<td>42 (19.4)</td>
</tr>
<tr>
<td>0-6 Months*</td>
<td>9 (4.1)</td>
<td>50 (23.1)</td>
</tr>
</tbody>
</table>

* For both Studies, p < 0.001 for treatment comparisons of cumulative GU incidence at 6 months.

In these trials, patients receiving naproxen and esomeprazole magnesium delayed-release tablets had a mean duration of therapy of 152 days compared to 124 days in patients receiving enteric-coated naproxen alone. A higher proportion of patients taking EC-naproxen (12%) discontinued the study due to upper GI adverse events (including duodenal ulcers) compared to naproxen and esomeprazole magnesium delayed-release tablets (4%) in both trials [see Adverse Reactions (6)].

The efficacy of naproxen and esomeprazole magnesium delayed-release tablets in treating the signs and symptoms of osteoarthritis was established in two 12-week randomized, double-blind, placebo-controlled trials in patients with osteoarthritis (OA) of the knee. In these two trials, patients were allowed to remain on low-dose aspirin for cardioprophylaxis. Naproxen and esomeprazole magnesium delayed-release tablets were given as 500 mg/20 mg twice daily. In each trial, patients receiving naproxen and
esomeprazole magnesium delayed-release tablets had significantly better results compared to patients receiving placebo as measured by change from baseline of the WOMAC pain subscale and the WOMAC physical function subscale and a Patient Global Assessment Score.

Based on studies with enteric-coated naproxen, improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease. In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest.

16 HOW SUPPLIED/STORAGE AND HANDLING

Naproxen and Esomeprazole Magnesium Delayed-Release Tablets are available containing 375 mg or 500 mg of naproxen, USP and 22.25 mg of esomeprazole magnesium, USP equivalent to 20 mg of esomeprazole providing for the following combinations: 375 mg/20 mg and 500 mg/20 mg.

The 375 mg/20 mg tablets are yellow, film-coated, oval, unscored tablets imprinted with NE1 in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-4385-93
bottles of 30 tablets

NDC 0378-4385-91
bottles of 60 tablets

NDC 0378-4385-77
bottles of 90 tablets

NDC 0378-4385-05
bottles of 500 tablets

The 500 mg/20 mg tablets are yellow, film-coated, oval, unscored tablets imprinted with NE2 in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-4386-93
bottles of 30 tablets

NDC 0378-4386-91
bottles of 60 tablets

NDC 0378-4386-77
bottles of 90 tablets

NDC 0378-4386-05
bottles of 500 tablets
17 PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients, families, or caregivers of the following before and during the course of ongoing therapy.

Cardiovascular Thrombotic Events: Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation: Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their healthcare provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Hepatotoxicity: Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop naproxen and esomeprazole magnesium delayed-release tablets and seek immediate medical therapy [see Warnings and Precautions (5.3)].

Heart Failure and Edema: Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

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), Warnings and Precautions (5.7)].

Serious Skin Reactions, Including DRESS: Advise patients to stop taking naproxen and esomeprazole magnesium delayed-release tablets immediately if they develop any type of rash or fever and contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9, 5.10)].

Fetal Toxicity: Inform pregnant women to avoid use of naproxen and esomeprazole magnesium delayed-release tablets and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closure of the fetal ductus arteriosus. If treatment with naproxen and esomeprazole magnesium delayed-release tablets is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may
need to be monitored for oligohydramnios [see Warnings and Precautions (5.11), Use in Specific Populations (8.1)].

**Infertility:** Advise females of reproductive potential that NSAIDs, including naproxen and esomeprazole magnesium delayed-release tablets, may be associated with reversible infertility [see Use in Specific Populations (8.3)].

**Gastric Malignancy:** Advise patients to return to their healthcare provider if they have gastric symptoms while taking naproxen and esomeprazole magnesium delayed-release tablets or after completing treatment [see Warnings and Precautions (5.17)].

**Acute Tubulointerstitial Nephritis:** Advise patients to report to their healthcare provider immediately if they experience a decrease in the amount they urinate or have blood in their urine [see Warnings and Precautions (5.18)].

**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 (5.19)].

**Bone Fracture:** Advise patients to report any sign or symptom of osteoporosis (e.g., recent bone fracture, low bone density) to their healthcare provider [see Warnings and Precautions (5.20)].

**Cutaneous and Systemic Lupus Erythematosus:** Advise patients to immediately call their healthcare provider to report any new or worsening of symptoms associated with cutaneous or systemic lupus erythematosus [see Warnings and Precautions (5.21)].

**Cyanocobalamin (Vitamin B-12) Deficiency:** Advise patients taking naproxen and esomeprazole magnesium delayed-release tablets 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 (5.23)].

**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 (5.24)].

**Drug Interactions:**

- Inform patients that the concomitant use of naproxen and esomeprazole magnesium delayed-release tablets with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.16), 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 (5.22, 5.25, 5.27)].
- Inform patients not to use low-dose aspirin concomitantly with naproxen and esomeprazole magnesium delayed-release tablets until they talk to their healthcare provider [see Drug Interactions (7)].

**Administration:**
• Inform patients that naproxen and esomeprazole magnesium delayed-release tablets should be swallowed whole with liquid. Tablets should not be split, chewed, crushed or dissolved. Naproxen and esomeprazole magnesium delayed-release 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 naproxen and esomeprazole magnesium delayed-release tablets.

Medication Guide

Naproxen and Esomeprazole Magnesium Delayed-Release Tablets
(na prox′ en es″ oh mep′ ra zole mag nee′ zee um)

What is the most important information I should know about naproxen and esomeprazole magnesium delayed-release tablets?

You should take naproxen and esomeprazole magnesium delayed-release tablets exactly as prescribed, at the lowest dose possible and for the shortest time needed.

Naproxen and esomeprazole magnesium delayed-release tablets may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your healthcare provider.

Naproxen and esomeprazole magnesium delayed-release tablets contain naproxen, a non-steroidal anti-inflammatory drug (NSAID) and esomeprazole magnesium, a proton pump inhibitor (PPI) medicine.

Naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

Avoid taking naproxen and esomeprazole magnesium delayed-release tablets after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you...
Talk to your healthcare provider about your risk of these serious side effects.

Naproxen and esomeprazole magnesium delayed-release tablets can have other serious side effects:

- 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 naproxen and esomeprazole magnesium delayed-release tablets. Some NSAIDs are sold in lower doses without a prescription (over-the-counter).

- A type of kidney problem (acute tubulointerstitial nephritis). Some people who take proton pump inhibitor (PPI) medicines, including naproxen and esomeprazole magnesium delayed-release tablets, may develop a kidney problem called acute tubulointerstitial nephritis that can happen at any time during treatment with naproxen and esomeprazole magnesium delayed-release tablets. 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 naproxen and esomeprazole magnesium delayed-release tablets, 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.

Naproxen and esomeprazole magnesium delayed-release tablets can have other serious
side effects. See “What are the possible side effects of naproxen and esomeprazole magnesium delayed-release tablets?”

What are naproxen and esomeprazole magnesium delayed-release tablets?

Naproxen and esomeprazole magnesium delayed-release tablets are 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets is used to:

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

It is not known if naproxen and esomeprazole magnesium delayed-release tablets are 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 naproxen and esomeprazole magnesium delayed-release tablets, because they will not work the same way.

Studies in people who take naproxen and esomeprazole magnesium delayed-release tablets have not extended past 6 months.

Do not take naproxen and esomeprazole magnesium delayed-release tablets:

- if you are allergic to naproxen, esomeprazole magnesium, omeprazole, any other PPI medicine, or any of the ingredients in naproxen and esomeprazole magnesium delayed-release tablets. See the end of this Medication Guide for a complete list of ingredients in naproxen and esomeprazole magnesium delayed-release tablets.
- 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 naproxen and esomeprazole magnesium delayed-release tablets, 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. Taking naproxen and esomeprazole magnesium delayed-release tablets at about 20 weeks of pregnancy or later may
Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets?

- Take naproxen and esomeprazole magnesium delayed-release tablets exactly as prescribed by your healthcare provider.
- Take 1 naproxen and esomeprazole magnesium delayed-release tablet 2 times each day.
- Take naproxen and esomeprazole magnesium delayed-release tablets at least 30 minutes before a meal.
- Swallow naproxen and esomeprazole magnesium delayed-release tablets whole with liquid. Do not split, chew, crush or dissolve naproxen and esomeprazole magnesium delayed-release tablets.
- You may use antacids while taking naproxen and esomeprazole magnesium delayed-release tablets.
- If you forget to take your dose of naproxen and esomeprazole magnesium delayed-release tablets, take it as soon as you remember. If it is almost time for
What are the possible side effects of naproxen and esomeprazole magnesium delayed-release tablets?

Naproxen and esomeprazole magnesium delayed-release tablets can cause serious side effects, including:

See “What is the most important information I should know about naproxen and esomeprazole magnesium delayed-release tablets?”

- 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets 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 naproxen and esomeprazole magnesium delayed-release tablets 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 many naproxen and esomeprazole magnesium delayed-release tablets, call your healthcare provider or get medical help right away.

These are not all the possible side effects of naproxen and esomeprazole magnesium delayed-release tablets. **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 naproxen and esomeprazole magnesium delayed-release tablets?

- Store naproxen and esomeprazole magnesium delayed-release tablets at room temperature between 20° to 25°C (68° to 77°F).
- Store naproxen and esomeprazole magnesium delayed-release tablets in the original container.
- Keep the bottle of naproxen and esomeprazole magnesium delayed-release tablets tightly closed to protect from moisture.

Keep naproxen and esomeprazole magnesium delayed-release tablets and all medicines out of the reach of children.

What are the ingredients in naproxen and esomeprazole magnesium delayed-release tablets?

**Active ingredients:** naproxen and esomeprazole magnesium

**Inactive ingredients:** acetylated monoglycerides, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, mono and diglycerides, polyethylene glycol, polysorbate 80, povidone, propylene glycol, sodium carbonate anhydrous, titanium dioxide, triethyl citrate and yellow iron oxide. The black imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol and shellac glaze.

**General information about the safe and effective use of naproxen and esomeprazole magnesium delayed-release tablets**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use naproxen and esomeprazole magnesium delayed-release tablets for a condition for which they were not prescribed. Do not give naproxen and esomeprazole magnesium delayed-release tablets to other people, even if they have the same symptoms that you have. They may harm them. You can ask your healthcare provider or pharmacist for information about naproxen and esomeprazole magnesium delayed-release tablets that is written for health professionals.
This Medication Guide has been approved by the U.S. Food and Drug Administration. The brands listed are trademarks of their respective owners.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured by:
Mylan Laboratories Limited
Hyderabad — 500 096, India

75079833
Revised: 5/2021
MX:NAESDR:R9mh/MX:MG:NAESDR:R8mh

PRINCIPAL DISPLAY PANEL – 375 mg/20 mg

NDC 0378-4385-93
Naproxen and
Esomeprazole
Magnesium Delayed-Release
Tablets
375 mg/
20 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only 30 Tablets

*Each film-coated tablet contains 375 mg of naproxen, USP and 22.25 mg of esomeprazole magnesium, USP equivalent to 20 mg of esomeprazole.

Usual Dosage: Take one tablet twice daily at least 30 minutes before meals. Tablets are to be swallowed whole with liquid. Do not split, chew, crush, or dissolve the tablet. See accompanying prescribing information.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture.

Manufactured for:
PRINCIPAL DISPLAY PANEL - 500 mg/20 mg

NDC 0378-4386-93
Naproxen and Esomeprazole
Magnesium Delayed-Release Tablets
500 mg/
20 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only 30 Tablets

*Each film-coated tablet contains 500 mg of naproxen, USP and 22.25 mg of esomeprazole magnesium, USP equivalent to 20 mg of esomeprazole.

Usual Dosage: Take one tablet twice daily at least 30 minutes before meals. Tablets are to be swallowed whole with liquid. Do not split, chew, crush, or dissolve the tablet. See accompanying prescribing information.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan.com

RMX4386H3

Keep this and all medication out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89
# NAPROXEN AND ESOMEPRAZOLE MAGNESIUM

naproxen and esomeprazole magnesium tablet, film coated

## Product Information

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## Active Ingredient/Active Moiety

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- **Score**: no score
- **Shape**: OVAL
- **Size**: 17mm
- **Flavor**: Imprint Code NE1

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**Marketing Information**

- **Marketing Category**: ANDA
- **Application Number or Monograph Citation**: ANDA204920
- **Marketing Start Date**: 11/22/2021

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**NAPROXEN AND ESOMEPRAZOLE MAGNESIUM**

naproxen and esomeprazole magnesium tablet, film coated

**Product Information**

- **Product Type**: HUMAN PRESCRIPTION DRUG
- **Item Code (Source)**: NDC:0378-4386
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**Labeler -** Mylan Pharmaceuticals Inc. (059295980)

Revised: 5/2021