NAPROXEN SODIUM—naproxen sodium tablets, film coated, extended release

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

- Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use, but the increased absolute risk is small, and may decrease with lower doses.
- Use of NSAIDs in the setting of coronary artery bypass graft (CABG) surgery is associated with increased cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Avoid use of NSAIDs for at least 10 days prior to CABG surgery.
- If NSAID therapy is necessary before 10 days after CABG surgery, use the lowest possible dose for the shortest possible time.
- Use of NSAIDs in the setting of CABG surgery increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation.

CONTRAINDICATIONS

- Hypersensitivity to any component of the product
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
- Intrahepatic cholestasis of pregnancy

WARNINGS AND PRECAUTIONS

- Gastrointestinal Toxicity: NSAIDs 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, likely in patients with coexisting conditions that increase risk. NSAIDs can deplete platelet function in severe cases of skin rash or other signs of hypersensitivity (e.g., anaphylaxis, angioedema, urticaria).
- Use in Patients with History of Asthma, Rhinitis, or Eczema: The use of NSAIDs in patients with these conditions may increase the risk of asthma-related events (including anaphylaxis), which can be life-threatening or fatal. Inform patients of the warning signs and symptoms of anaphylaxis. Discontinue if an anaphylactic reaction occurs.
- Use in Patients with Hypertension: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Patients with hypertension are at increased risk of these events, particularly patients with severe hypertension. Consider decreasing the dose of concomitant diuretics or increasing the dose of a diuretic in patients with severe hypertension. NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics.
- Use in Patients with Congestive Heart Failure: NSAIDs can worsen fluid retention and causing an increase in blood pressure in patients with congestive heart failure. NSAIDs can reduce sodium excretion in patients with heart failure, which may offset antihypertensive effects of diuretics and vasodilators in these patients. Use NSAIDs with caution in patients with congestive heart failure.
- Use in Patients with Gastrointestinal Toxicity: NSAIDs can cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. NSAIDs can deplete platelet function in severe cases of skin rash or other signs of hypersensitivity (e.g., anaphylaxis, angioedema, urticaria).
- Use in Patients with Asthma: NSAIDs can cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Patients with asthma are at an increased risk of these events. NSAIDs can deplete platelet function in severe cases of skin rash or other signs of hypersensitivity (e.g., anaphylaxis, angioedema, urticaria).
- Use in Patients with Renal Impairment: NSAIDs can cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Patients with renal impairment, including those with renal insufficiency or renal failure, and those taking diuretics have a higher risk of these events. NSAIDs can cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Use the lowest possible dose for the shortest possible time in patients with renal impairment.

DOSE AND ADMINISTRATION

- Use of NSAIDs in the treatment of osteoarthritis (OA) is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min), history of gout, who are hypertensive, or who are taking aspirin or other NSAIDs. These patients may have an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal.
- Management of Pain, PD, and Acute Tendinitis and Bursitis: The dosage is two 500 mg tablets once daily. For patients with severe pain, take two 500 mg tablets twice daily.
- Management of RA, OA, and AS: The dosage is two 375 mg or 500 mg tablets once daily, or one 750 mg tablet once daily.
- Management of Pain, PD, and Acute Tendinitis and Bursitis: The dosage is two 500 mg tablets once daily. For patients with severe pain, take two 500 mg tablets twice daily.
- Management of RA, OA, and AS: The dosage is two 375 mg or 500 mg tablets once daily, or one 750 mg tablet once daily.

DRUG INTERACTIONS

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WARNINGS AND PRECAUTIONS

- Gastrointestinal Toxicity: NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. NSAIDs can deplete platelet function in severe cases of skin rash or other signs of hypersensitivity (e.g., anaphylaxis, angioedema, urticaria).
- Use in Patients with History of Asthma, Rhinitis, or Eczema: The use of NSAIDs in patients with these conditions may increase the risk of asthma-related events (including anaphylaxis), which can be life-threatening or fatal. Inform patients of the warning signs and symptoms of anaphylaxis. Discontinue if an anaphylactic reaction occurs.
- Use in Patients with Hypertension: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Patients with hypertension are at increased risk of these events, particularly patients with severe hypertension. Consider decreasing the dose of concomitant diuretics or increasing the dose of a diuretic in patients with severe hypertension. NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics.
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- Use in Patients with Gastrointestinal Toxicity: NSAIDs can cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. NSAIDs can deplete platelet function in severe cases of skin rash or other signs of hypersensitivity (e.g., anaphylaxis, angioedema, urticaria).
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INDICATIONS AND USAGE

- NAPROXEN SODIUM CONTROLLED-RELEASE TABLETS are a nonsteroidal anti-inflammatory drug indicated for the treatment of:
  - Management of Pain, PD, and Acute Tendinitis and Bursitis
  - Management of RA, OA, and AS

NAPROXEN SODIUM CONTROLLED-RELEASE TABLETS are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without a history of aspirin sensitivity) for the development of asthma. For the management of pain, PD, and acute gout:

- Management of Pain, PD, and Acute Tendinitis and Bursitis: The dosage is two 500 mg tablets once daily. For patients with severe pain, take two 500 mg tablets twice daily.
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- Management of RA, OA, and AS: The dosage is two 375 mg or 500 mg tablets once daily, or one 750 mg tablet once daily.
10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first
CV thrombotic events associated with NSAID use. The concurrent use of
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious
events and the steps to take if they occur.

risk has been observed most consistently at higher doses.

thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic
events, including myocardial infarction (MI) and stroke, 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)].

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of Naproxen Sodium Controlled-Release Tablets and other treatment options before deciding to use Naproxen Sodium Controlled-Release Tablets. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

After observing the response to initial therapy with Naproxen Sodium Controlled-Release Tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

2.2 Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

The recommended starting dose of Naproxen Sodium Controlled-Release Tablets is 500 mg tablets (1,000 mg) once daily, or two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily. Patients already taking naproxen 250 mg, 375 mg, or 500 mg twice daily (morning and evening) may have their total daily dose replaced with Naproxen Sodium Controlled-Release Tablets as a single daily dose.

During long-term administration, the dose of Naproxen Sodium Controlled-Release Tablets may be adjusted up or down depending on the clinical response of the patient. In patients who tolerate lower doses of Naproxen Sodium Controlled-Release Tablets well, the dose may be increased to two Naproxen Sodium Controlled-Release 750 mg tablets (1,500 mg) or three Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily. Patients with known CV disease or risk factors for CV disease.  However, patients with known CV disease or risk factors for CV disease also had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline risk. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first week of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for adverse CV events 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)].

Naproxen Sodium Controlled-Release Tablets are contraindicated in the setting of cayor artery bypass graft (CABG) surgery [see Contraindications (6) and Warnings and Precautions (5.1)].

Naproxen Sodium Controlled-Release Tablets are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen or any component of the drug product [see Warnings and Precautions (5.5)].

- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, even fatal, anaphylactic reactions to these drugs have been reported in such patients [see Warnings and Precautions (5.1)].

- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]

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 risk. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first week of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

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)].

4.8 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 revascularization, 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 the next four years of follow-up.

Avoid the use of Naproxen Sodium Controlled-Release Tablets in patients with recent MI unless the benefits are expected to outweigh the risk of recurrent CV-related events. If Naproxen Sodium Controlled-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, 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 of 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 poorer general health status. Most postmarketing reports of fatal GI events occurred 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.
- Recommend use of a non-drug therapy (e.g., proton pump inhibitors, H2 blockers) in patients who are at increased risk for GI bleeding.
- Recommend discontinuation of NSAIDs in patients with active GI bleeding.
- In the setting of concomitant use of low-dose aspirin for cardiovascular prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 3% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (three or more times ULN) may occur in up to 15% of patients treated with NSAIDs including naproxen. Inform patients of the warning signs and symptoms of hepatic injury (e.g., nausea, fatigue, anorexia, 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 Sodium Controlled-Release Tablets immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including Naproxen Sodium Controlled-Release Tablets, can lead to new-onset 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, diuretics, or angiotensin receptor blockers (ARBs) should be evaluated for hypertension, and if present, the dose of the ACE inhibitor or ARB should be reduced before initiating treatment with Naproxen Sodium Controlled-Release Tablets [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 Cochrane and traditional NSAID Trials' Collaborative meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalization for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In the Danish National Registry study of patients with heart failure, NSAIDs 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 other therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of worsening heart failure. If Naproxen Sodium Controlled-Release Tablets is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hypertension

Renal Function

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 NSAIDs 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 toxic reaction are those with impaired renal function, dehydration, hypotension, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery of the pre-existing state.

No information is available from controlled clinical studies regarding the use of Naproxen Sodium Controlled-Release Tablets in patients with advanced renal disease. The renal effects of Naproxen Sodium Controlled-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 Sodium Controlled-Release Tablets. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Naproxen Sodium Controlled-Release Tablets [see Drug Interactions (7)]. Avoid the use of Naproxen Sodium Controlled-Release Tablets in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Naproxen Sodium Controlled-Release Tablets are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hypertension

Increases intrarenal resistance, including hypertension, 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 hyperreninemic-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 (5.5)]. Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subgroup 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 exists among aspirin and other NSAIDs, patients who have had an anaphylactic reaction to aspirin or other NSAIDs may have a similar reaction to naproxen.

If aspirin sensitivity is suspected, Naproxen Sodium Controlled-Release Tablets are contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When Naproxen Sodium Controlled-Release Tablets are used in patients with preexisting 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 reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Information about the signs and symptoms of serious skin reactions, and to discontinue the use of Naproxen Sodium Controlled-Release Tablets at the first appearance of skin rash or any other sign of hypersensitivity.

Naproxen sodium is contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus

Naproxen may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Naproxen Sodium Controlled-Release Tablets, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (8.1)].

5.11 Hematologic Toxicity

Amenorrhea has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on ovulation. If a patient treated with Naproxen Sodium Controlled-Release Tablets has any sign or symptom of amenorrhea, monitor hemoglobin and hematocrit.

NSAIDs, including Naproxen Sodium Controlled-Release Tablets, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concurrent use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

5.12 Masking of Inflammation and Fever

The pharmacological activity of Naproxen Sodium Controlled-Release Tablets in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infection.

5.13 Laboratory Monitoring

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

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 (5.2)]
- GI Bleeding, Ulceration and Perforation [see Warnings and Precautions (5.2)]
- Respiratory: Ulcerative colitis, spontaneous perforation [see Warnings and Precautions (5.4)]
- Renal: Acute kidney injury [see Warnings and Precautions (5.5)]
- Endocrine: Hyperkalemia [see Warnings and Precautions (5.6)]

The most frequent adverse reactions occurring in less than 3% of patients are unmarked.

Incidence greater than 1% (probable causal relationship)

Body as a Whole—Pain
digestion, malaise, abdominal pain, back pain, arthralgia, joint pain, lightheadedness
CNS and Peripheral Nervous System—Dizziness, somnolence, vertigo, headache, paresthesia
Skin and Appendages—Pruritus, dermatitis, rash
Urinary System—Dysuria, hematuria, proteinuria, urinary tract infection
Other—Anemia, agranulocytosis, agranulocytosis, neutropenia

Incidence less than 1% (probable causal relationship)

Body as a Whole—Asthma, chest pain, dyspnea, urinary tract infection, orthostatic hypotension, cough
CNS and Peripheral Nervous System—Dizziness, paresthesia, headache, insomnia, tremor, somnolence
Skin and Appendages—Pruritus, dermatitis, rash, alopecia, photosensitivity
Other—Anemia, agranulocytosis, agranulocytosis, neutropenia

Incidence less than 1% (probable causal relationship)

Body as a Whole—Asthma, chest pain, dyspnea, urinary tract infection, orthostatic hypotension, cough
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6.1 Clinical Trial Experience

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.

As with all drugs used in this class, the frequency and severity of adverse events depends on several factors: the dose of the drug and duration of treatment; the age, sex, physical condition of the patient; any concurrent medical diagnosis or individual risk factors. The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between drug usage and the adverse event. These reactions listed in “Probable Causal Relationship” there is at least one case for each adverse reaction where there is evidence to suggest there is a causal relationship between drug usage and the reported event. The adverse reactions reported were based on the results from two double-blind clinical trials of three months duration with an additional nine month open-label extension. A total of 562 patients received Naproxen Sodium Controlled-Release Tablets either in the double-blind period or in the nine month open-label extension. Of these 562 patients, 252 received Naproxen Sodium Controlled-Release Tablets, 167 were initially treated with Naprosyn® and 143 were initially treated with placebo. Adverse reaction reports from patients who received Naproxen Sodium Controlled-Release Tablets were shown by body system.

These adverse reactions observed with naproxen but not reported in controlled trials with Naproxen Sodium Controlled-Release Tablets are included.

5.14 Neutropenia

Those reactions occurring in less than 3% of the patients are unmarked.

5.15 Anaphylactic Reactions

The most frequent adverse events from the double-blind and open-label clinical trials were headache (3%), followed by dyspepsia (1.4%), and headache (1%). The incidence of other adverse events occurring in 1% to 5% of the patients are marked with an asterisk.

6.2 Drug Interactions

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.

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

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Drug/Laboratory Test Interaction

See Table 1 for clinically significant drug interactions with naproxen.

Table 1: Clinically Significant Drug Interactions with Naproxen

**Drugs That Interfere with Hemostasis**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concurrent use of naproxen and anticoagulants has an increased risk of serious bleeding compared to the use of either drug alone.</td>
<td>Naproxen with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin reuptake inhibitors (SSRIs) for signs of bleeding</td>
<td>Monitor patients with concurrent use of naproxen sodium with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin reuptake inhibitors (SSRIs) for signs of bleeding</td>
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**Aspirin**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled clinical studies showed that the concurrent use of NSAIDs and aspirin doses of anticoagulants do not produce any greater therapeutic effects than the use of NSAIDs alone. In a clinical study, the concurrent use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reaction as compared to the use of the NSAID alone</td>
<td>Concurrent use of naproxen sodium and aspirin is not generally recommended because naproxen sodium is a substitute for low dose aspirin for cardiovascular protection</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers (including propranolol).</td>
<td>During concomitant use of naproxen sodium and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.</td>
<td>During concurrent use of naproxen sodium and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained</td>
</tr>
</tbody>
</table>

**Diabetes**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>The concomitant use of metformin and a sulfonylurea or biguanide may increase the risk for lactic acidosis (see Warnings and Precautions (5.6)).</td>
<td>During concurrent use of naproxen sodium and diabetics, observe patients for signs of worsening renal function, in addition to assessing diuretic efficacy including antihypertensive effects</td>
<td>During concurrent use of naproxen sodium and diabetics, observe patients for signs of worsening renal function, in addition to assessing diuretic efficacy including antihypertensive effects</td>
</tr>
</tbody>
</table>

**Digestion**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs have produced elevation in plasma lithium levels and reductions in renal lithium clearance. The mean maximum lithium concentration increased 15%, and the renal clearance decreased by approximately 25%. This effect has been attributed to NSAID inhibition of renal proximal tubular sodium reabsorption.</td>
<td>During concurrent use of naproxen sodium and lithium, monitor for signs of lithium toxicity.</td>
<td>During concurrent use of naproxen sodium and lithium, monitor for signs of lithium toxicity</td>
</tr>
</tbody>
</table>

**Methotrexate**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).</td>
<td>During concurrent use of naproxen sodium and methotrexate, monitor patients for methotrexate toxicity.</td>
<td>During concurrent use of naproxen sodium and methotrexate, monitor patients for methotrexate toxicity</td>
</tr>
</tbody>
</table>

**Cyclosporine**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs and cyclosporine may increase cyclosporine’s nephrotoxicity.</td>
<td>During concurrent use of naproxen sodium and cyclosporine, monitor patients for signs of worsening renal function.</td>
<td>During concurrent use of naproxen sodium and cyclosporine, monitor patients for signs of worsening renal function</td>
</tr>
</tbody>
</table>

**NSAIDs and Salicylates**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of NSAIDs and salicylates (e.g., aspirin, ibuprofen) increases the risk of GI toxicity, with little or no increase in efficacy (see Warnings and Precautions (5.2)).</td>
<td>The concomitant use of aspirin with other NSAIDs or salicylates is not recommended.</td>
<td>The concomitant use of aspirin with other NSAIDs or salicylates is not recommended</td>
</tr>
</tbody>
</table>

**Probenecid**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>During concurrent use of naproxen sodium and probenecid, monitor patients with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
<td>During concurrent use of naproxen sodium and probenecid, monitor patients with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
<td>During concurrent use of naproxen sodium and probenecid, monitor patients with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
</tr>
</tbody>
</table>

**Amoxicillin and Sulfa-Cotrimoxazole**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>During concurrent use of amoxicillin or sulfa-cotrimoxazole, monitor patients with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
<td>During concurrent use of amoxicillin or sulfa-cotrimoxazole, monitor patients with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
<td>During concurrent use of amoxicillin or sulfa-cotrimoxazole, monitor patients with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity.</td>
</tr>
</tbody>
</table>

**Cholestyramine**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant administration of amoxicillin or sulfa-cotrimoxazole can delay the absorption of naproxen.</td>
<td>Concomitant administration of amoxicillin or sulfa-cotrimoxazole can delay the absorption of naproxen.</td>
<td>Concomitant administration of amoxicillin or sulfa-cotrimoxazole can delay the absorption of naproxen</td>
</tr>
</tbody>
</table>

**Probenecid**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probenecid may concurrently increase naproxen aminoglutethimide levels and extend its plasma half-life significantly.</td>
<td>Probenecid may concurrently increase naproxen aminoglutethimide levels and extend its plasma half-life significantly.</td>
<td>Probenecid may concurrently increase naproxen aminoglutethimide levels and extend its plasma half-life significantly.</td>
</tr>
</tbody>
</table>

**Other antihistamines**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen may increase plasma levels of other antihistamines.</td>
<td>Naproxen may increase plasma levels of other antihistamines.</td>
<td>Naproxen may increase plasma levels of other antihistamines.</td>
</tr>
</tbody>
</table>

**Drug/Laboratory Test Interactions**

**Bleeding times**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen may decrease platelet aggregation and prolong bleeding time.</td>
<td>Naproxen may decrease platelet aggregation and prolong bleeding time.</td>
<td>Naproxen may decrease platelet aggregation and prolong bleeding time.</td>
</tr>
</tbody>
</table>

**Serum creatinine**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Drug/Other</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>The administration of naproxen may result in increased urinary values for 17-ketosteroids because of an interaction between the drug and its metabolites with renin-angiotensin system.</td>
<td>The administration of naproxen may result in increased urinary values for 17-ketosteroids because of an interaction between the drug and its metabolites with renin-angiotensin system.</td>
<td>The administration of naproxen may result in increased urinary values for 17-ketosteroids because of an interaction between the drug and its metabolites with renin-angiotensin system.</td>
</tr>
</tbody>
</table>

*Although 15-hydroxy-prostaglandin E2 (15-HETE) is not an anti-inflammatory enzyme, it is suggested that therapy with naproxen*
Naproxen Sodium Controlled-Release Tablets contain 412.5 mg of naproxen sodium, equivalent to 375 mg of naproxen, and 37.5 mg sodium. Each Naproxen Sodium Controlled-Release Tablets also contain the following inactive ingredients: ammoniomethacrylate copolymer Type A, equivalent to 375 mg of naproxen, and 37.5 mg sodium.

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Each Naproxen Sodium Controlled-Release Tablets contains 412.5 mg of naproxen sodium, equivalent to 375 mg of naproxen, and 37.5 mg sodium. Each Naproxen Sodium Controlled-Release Tablets also contain the following inactive ingredients: ammoniomethacrylate copolymer Type A.

The safety and effectiveness of naproxen sodium in pediatric populations has not been established.

Based on animal data, prostaglandin synthesis inhibitors such as naproxen sodium resulted in increased pre- and post-implantation loss. Use of NSAIDs, including naproxen sodium, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including naproxen sodium, in pregnant women starting at 30 weeks of gestation (third trimester).

There are an adequate and well-controlled studies of naproxen sodium in pregnant women.

Data from observational studies regarding potential embryotoxic effects of NSAID use in women in the first trimester of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction studies in rats, rabbits, and mice, no evidence of teratogenicity or fetal harm with naproxen sodium administered during the period of organogenesis at doses 0.13, 0.26, and 0.6 times the maximum recommended human daily dose of 1,500 mg daily, respectively.

Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water. Its molecular formula is C\(_{11}\)H\(_{17}\)NO\(_2\), and it has the following chemical structure.

\[
\text{C}_11\text{H}_{17}\text{NO}_2
\]

Clinical Pharmacology (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)
ammonium cellulose, copolymer Type B, citric acid, crospovidone, magnesium stearate, methacrylic acid copolymer Type A, microcrystalline cellulose, prelube, and talc. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naproxen has anti-inflammatory, anti-inflammatory, and antipyretic properties.

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

Naproxen sodium is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen sodium concentration reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of neuropeptides in inducing pain in animal models.

Prostaglandins are mediators of inflammation. Because naproxen sodium is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandin peripheral tissues.

12.2 Pharmacokinetics

Although naproxen itself is well absorbed, the sodium salt form is more rapidly absorbed, resulting in higher peak plasma levels for a given dose. Approximately 30% of the total naproxen sodium dose in Naproxen Sodium Controlled-Release Tablets is present in the dosage form as an immediate release component. The remaining naproxen sodium is coated as microspheres to provide sustained release properties. After oral administration, plasma levels of naproxen are detected within 30 minutes of dosing, with peak plasma levels occurring approximately 5 hours after dosing. The observed terminal elimination half-life of naproxen from both immediate release naproxen sodium and Naproxen Sodium Controlled-Release Tablets is approximately 15 hours. Steady state levels of naproxen are achieved in 3 days and the degree of naproxen accumulation in the blood is consistent with this.

Plasma Naproxen Concentrations Mean of 24 Subjects (1 to 2SD) (Steady State, Day 5)

![Graph showing plasma naproxen concentrations](image)

### Pharmacokinetic Parameters at Steady State Day 5 (Mean of 24 Subjects)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>naproxen 500 mg Q12h/5 days (1000 mg)</th>
<th>Naproxen Sodium Controlled-Release 2 x 500 mg tablets (1000 mg) Q24h/5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (mcg/mL)</td>
<td>1446 ± 168</td>
<td>1448 ± 145</td>
</tr>
<tr>
<td>Range (mcg/mL)</td>
<td>1167 - 1668</td>
<td>1417 - 1774</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>1 - 4</td>
<td>23 - 48</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>94</td>
<td>60 - 90</td>
</tr>
<tr>
<td>AUC 0-24 h (mg/hr/L)</td>
<td>7 - 117</td>
<td>60 - 90</td>
</tr>
<tr>
<td>Ctrough (mcg/mL)</td>
<td>6</td>
<td>13 - 51</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>36</td>
<td>7 - 23</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>3</td>
<td>1 - 4</td>
</tr>
</tbody>
</table>

### Absorption

Naproxen is rapidly and completely absorbed from the GI tract with an bioavailability of 95%. Based on the pharmacokinetic profile, the absorption phase of Naproxen Sodium Controlled-Release Tablets occurs in the first 4-6 hours after administration. This coincides with dissolution of the tablet in the stomach, the mixing of the sustained release microspheres through the small intestine and the prolonged large intestine. A radiolabeled imaging study has been performed in healthy volunteers that confirm rapid dissolution of the intact matrix and absorption of the microspheres.

The absorption rate from the sustained release particulate component of Naproxen Sodium Controlled-Release Tablets is slower than that for conventional naproxen sodium tablets. It is this prolongation of drug absorption processes that maintain plasma levels and allows for once daily dosing.

### Food Effects

No significant food effects were observed when twenty-four subjects were given a single dose of Naproxen Sodium Controlled-Release Tablets 500 mg either after an overnight fast or 30 minutes after a meal. In common with conventional naproxen and sodium formulations, food causes a slight decrease in the rate of naproxen absorption following Naproxen Sodium Controlled-Release Tablets administration.

### Elimination

Naproxen is extensively metabolized to 6-O-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

### Excretion

The elimination half-life of Naproxen Sodium Controlled-Release Tablets and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2 to 3 doses of Naproxen Sodium Controlled-Release Tablets. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 5%), 6-O-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (60 to 32%). A small amount (<5%) of the drug is excreted in the feces. The rate of excretion has been found to be linearly related to the rate of clearance from the plasma. In patients with renal failure, metabolites may accumulate.

### Specific Populations

#### Pediatric

No pediatric studies have been performed with Naproxen Sodium Controlled-Release Tablets, thus safety of Naproxen Sodium Controlled-Release Tablets in pediatric population has not been established.

### Hepatic Impairment

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma protein (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

### Renal Impairment

Naproxen pharmacokinetics have not been determined in subjects with renal insufficiency. Given that naproxen is metabolized and conjugates are primarily excreted by the kidneys, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min). (See Warnings and Precautions (5.6)).

### Drug Interactions

### Anticoagulant (oral)

When NSAIDs were administered with aspirin, the prothrombin time of patients receiving oral anticoagulants was not altered, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 1 for clinically significant drug interactions of NSAIDs with aspirin [see Drug Interactions (7)].

23 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>naproxen 500 mg Q12h/5 days (1000 mg)</th>
<th>Naproxen Sodium Controlled-Release 2 x 500 mg tablets (1000 mg) Q24h/5 days</th>
</tr>
</thead>
</table>
CONTRAINDICATIONS
A two year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8 mg/kg/day, 16 mg/kg/day, and 25 mg/kg/day (0.05, 0.1, and 0.16 times the maximum recommended human daily dose of 1,000 mg/day based on body surface area comparison). No evidence of tumorigenicity was found.

WARNINGS
Studies to evaluate the oncogenic potential of Naprosyn Suspension have not been completed.

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

14 CLINICAL STUDIES

PHYLLARYL ARTHRITIS
The use of Naproxen Sodium Controlled-Release Tablets for the management of the signs and symptoms of rheumatoid arthritis was assessed in a 12 week double-blind, randomized, placebo, and active-controlled study in 348 patients. Two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily and naproxen 500 mg tablets twice daily (1,000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study.

Glomerulonephritis
The use of Naproxen Sodium Controlled-Release Tablets for the management of the signs and symptoms of chronic nephritis of the base was assessed in a 12 week double-blind, placebo, and active-controlled study in 347 patients. Two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily and naproxen 500 mg tablets twice daily (1,000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study.

Anaphylaxis
The onset of the anaphylactic effect of Naproxen Sodium Controlled-Release Tablets was seen within 30 minutes in a pharmacologic/pharmacodynamic study of patients with pain following oral surgery. In controlled clinical trials, naproxen has been used in combination with gold, D-penicillamine, methotrexate, and corticosteroids. Its use in combination with salicylate is not recommended because there is evidence that aspirin increases the risk of bleeding and failure to adequately demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, with other NSAIDs the combination may result in higher frequency of adverse events that are demonstrated for either product alone.

Special Studies
In a double-blind randomized, parallel group study, 19 subjects received either two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily or naproxen 500 mg tablets (1,000 mg) twice daily for 7 days. Macular hole scores and endothelial scores were lower in the subjects who received Naproxen Sodium Controlled-Release Tablets. In another double-blind, randomized, crossover study, 23 subjects received two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily, naproxen 500 mg tablets (1,000 mg) twice daily and aspirin 650 mg four times daily (2,600 mg) for 7 days each. There were significantly fewer duodenal erosions seen with Naproxen Sodium Controlled-Release Tablets than with either aspirin or aspirin. There were significantly fewer gastric erosions with both Naproxen Sodium Controlled-Release Tablets and naproxen than with aspirin.

The clinical significance of these findings is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING
Naproxen sodium 375 mg are controlled-release tablets supplied as:

375 mg white, capsule-shaped tablets with “N” on one side and “375” on the reverse; In bottles of 100, NDC 06420-1375-1. Each tablet contains 412.5 mg naproxen sodium equivalent to 375 mg naproxen.

Storage
Store at room temperature, 20° to 25°C (68° to 77°F), excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

PREScribing INFORMATION

17 PATIENT COUNSELING INFORMATION
Advises the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with naproxen sodium and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advises 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 health care provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation
Naproxen sodium, like other NSAIDs, cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Advise patients to report symptoms of ulceraion and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. As with other NSAIDs, the concomitant use of low-dose aspirin for cardiac prophylaxis may increase the risk of upper gastrointestinal bleeding [see Warnings and Precautions (5.3)].

Hepatotoxicity
Inform patients of the warning sign and symptoms of hepatic toxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop naproxen sodium 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 Reaction
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7)].

Serious Skin Reactions
Naproxen sodium, like other NSAIDs, cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalization and even death. Advise patients to stop naproxen sodium immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.8)].

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including naproxen sodium, may be associated with a reversible delay in ovulation [see Use in Specific Populations (8.4)].

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

Avoid Concurrent Use of NSAIDs
Inform patients that the concurrent use of naproxen sodium with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and life or in increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7)].

Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concurrently with naproxen sodium until they talk to their healthcare provider [see Drug Interactions (7)].

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Manufactured for:
SAX, LLC
Los Angeles, CA 90064
PI735-0
Rev. 04/2019
Medication Guide for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAIDs 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 NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

- Should taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- Increased risk of bleeding, ulcers, and tears (perforations) 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 "coumadin," "warfarin," or "Coumadin®"
- longer use of NSAIDs
- smoking
- drinking alcohol

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or any other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

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

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 20 weeks of pregnancy.
- are breastfeeding or plan to breastfeed

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins, or herbal supplements. NSAIDs 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.

What is the possible side effects of NSAIDs? NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?" for more information.

What are the possible side effects of NSAIDs? NSAIDs can cause serious side effects, including:

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

General information about the safe and effective use of NSAIDs

NSAIDs are sometimes prescribed for purposes other than those listed in this Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured for:
SAL, LLC
Los Angeles, CA 90064
For more information, call 1-888-495-6078

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PRINCIPAL DISPLAY PANEL
NDC: 0342-1375-11
Naproxen Sodium
Controlled-Release Tablets
375 mg
Rx Only
100 Tablets

NAPROXEN SODIUM
Naproxen sodium tablets, film coated, extended release

Product Information
Product Type: ORAL PRESCRIPTION DRUG 
Non Code (Generic): NAPROXEN 375 mg 
NDC: 69420-375-00

Active Ingredient/Active Mailing
Ingredient Name: NAPROXEN SODIUM

Inactive Ingredients
Ingredient Name: CROSPOVIDONE (15 MPA.S AT 5%)
CITRIC ACID MONOHYDRATE 
AMMONIO METHACRYLATE COPOLYMER TYPE B

Strength
NAPROXEN SODIUM 375 mg
Product Characteristics

<table>
<thead>
<tr>
<th>Color</th>
<th>Score</th>
<th>Shape</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>None</td>
<td>Capsule</td>
<td>15mm</td>
</tr>
</tbody>
</table>

Flavor

Imprint Code

N;375

Contains

Packaging

<table>
<thead>
<tr>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100 in 1 BOTTLE; Type: NOT a Combination Product</td>
<td>05/01/2019</td>
<td>05/01/2019</td>
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</tbody>
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Marketing Information

Marketing Category

NDA AUTHORIZED GENERIC

Application Number or Monograph Citation

NDA020353

Marketing Start Date

05/01/2019

Labeler

SA3, LLC

Revised: 4/2019