NAPROXEN SODIUM- naproxen sodium tablet, film coated, extended release
SA3, LLC

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

NAPROXEN SODIUM Controlled-Release Tablets, for oral use
Initial U.S. Approval: 1976

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Nonsteroidal 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 Sodium Controlled-Release Tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **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. 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)**

INDICATIONS AND USAGE

Naproxen Sodium Controlled-Release Tablets is a nonsteroidal anti-inflammatory drug indicated for the treatment of:

- rheumatoid arthritis (RA)(1)
- osteoarthritis (OA)(1)
- ankylosing spondylitis (AS)(1)
- tendinitis, bursitis (1)
- acute gout (1)
- primary dysmenorrhea (PD)(1)
- the relief of mild to moderate pain (1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2)
- 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 requiring greater analgesic benefit, two 750 mg tablets or three 500 mg tablets may be used for a limited period. Thereafter, the total daily dose should not exceed two 500 mg tablets
- For the treatment of Acute Gout: The dosage is two to three 500 mg tablets once daily on the first day, followed by two 500 mg tablets once daily, until the attack has subsided.

DOSAGE FORMS AND STRENGTHS

Naproxen Sodium Controlled-Release Tablets: 375 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to naproxen or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

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 Sodium Controlled-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 Sodium Controlled-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 Sodium Controlled-Release Tablets are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue Naproxen Sodium Controlled-Release Tablets at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

ADVERSE REACTIONS

The most frequent adverse events were headache (15%), followed by dyspepsia (14%), and flu syndrome (10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, SA3, LLC at 1-888-495-6078 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking Naproxen Sodium Controlled-Release Tablets with drugs that interfere with hemostasis. Concomitant use of Naproxen Sodium Controlled-Release Tablets and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with Naproxen Sodium Controlled-Release Tablets may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with Naproxen Sodium Controlled-Release Tablets in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with Naproxen Sodium Controlled-Release Tablets can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)
Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of Naproxen Sodium Controlled-Release Tablets in women who have difficulties conceiving (8.3)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Instructions
2.2 Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis
2.3 Management of Pain, Primary Dysmenorrhea, and Acute Tendinitis and Bursitis
2.4 Acute Gout
2.5 Dosage Adjustments in Patients with Hepatic Impairment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Thrombotic Events
5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
5.3 Hepatotoxicity
5.4 Hypertension
5.5 Heart Failure and Edema
5.6 Renal Toxicity and Hyperkalemia
5.7 Anaphylactic Reactions
5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
5.9 Serious Skin Reactions
5.10 Premature Closure of Fetal Ductus Arteriosus
5.11 Hematologic Toxicity
5.12 Masking of Inflammation and Fever
5.13 Laboratory Monitoring
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal 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 *[see Warnings and Precautions (5.1)]*.**
- **Naproxen Sodium Controlled-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 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 Sodium Controlled-Release Tablets are indicated for the treatment of:

- rheumatoid arthritis (RA)
- osteoarthritis (OA)
- ankylosing spondylitis (AS)
- tendinitis, bursitis
- acute gout
- primary dysmenorrhea (PD)
- the relief of mild to moderate pain

[*see Warnings and Precautions (5)*].

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 in adults is two Naproxen Sodium Controlled-Release 375 mg tablets (750 mg) once daily, one Naproxen Sodium Controlled-Release 750 mg (750 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 (1,500 mg) once daily for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating patients, especially at the higher dose levels, the physician should observe sufficient increased clinical benefit to offset the potential increased risk [*see Clinical Pharmacology (12.3)*]. The lowest effective dose should be sought and used in every patient. Symptomatic improvement in arthritis usually begins within one week; however, treatment for two weeks may be required to achieve a therapeutic benefit.

2.3 Management of Pain, Primary Dysmenorrhea, and Acute Tendinitis and Bursitis

The recommended starting dose is two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily. For patients requiring greater analgesic benefit, two Naproxen Sodium Controlled-Release 750 mg tablets (1,500 mg) or three Naproxen Sodium Controlled-Release 500 mg tablets (1,500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg).

2.4 Acute Gout

The recommended dose on the first day is two to three Naproxen Sodium Controlled-Release 500 mg tablets (1,000 to 1,500 mg) once daily, followed by two Naproxen Sodium Controlled-Release 500 mg tablets (1,000 mg) once daily, until the attack has subsided.

2.5 Dosage Adjustments in Patients with Hepatic Impairment

A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients [*see Warnings and Precautions (5.3)*]. 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.

3 DOSAGE FORMS AND STRENGTHS

Naproxen Sodium Controlled-Release Tablets are available as follows:

375 mg: white, capsule-shaped tablet with "N" on one side and "375" on the reverse. Each tablet contains 412.5 mg naproxen sodium equivalent to 375 mg naproxen.

4 CONTRAINDICATIONS

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 components of the drug product *[see Warnings and Precautions (5.7, 5.9)]*
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.7, 5.8)]*
- *In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, 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 of follow-up.

Avoid the use of Naproxen Sodium Controlled-Release Tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic 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 to 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 poor 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.
- 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 Sodium Controlled-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)]*.

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% 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 (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 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, thiazide 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 Sodium Controlled-Release Tablets in patients with severe heart failure unless the benefits are expected to outweigh the 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 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 is usually followed by recovery to the pretreatment 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 preexisting 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 mused 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 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. Inform patients 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

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 Sodium Controlled-Release Tablets has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including Naproxen Sodium Controlled-Release Tablets, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) 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 infections.

5.13 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 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 (5.1)*]
- GI Bleeding, Ulceration and Perforation [*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)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials 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 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, the sex, physical condition of the patient; any concurrent medical diagnoses 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 these adverse events. In those reactions listed as “Probable Causal Relationship” there is at least one case for each adverse reaction where there is evidence to suggest that 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 controlled clinical trials of three months duration with an additional nine month open-label extension. A total of 542 patients received Naproxen Sodium Controlled-Release Tablets either in the double-blind period or in the nine month open-label extension. Of these 542 patients, 232 received Naproxen Sodium Controlled-Release Tablets, 167 were initially treated with Naprosyn® and 143 were initially treated with placebo. Adverse reactions reported by patients who received Naproxen Sodium Controlled-Release Tablets are shown by body system. Those adverse reactions observed with naproxen but not reported in controlled trials with Naproxen Sodium Controlled-Release Tablets are *italicized*.

The most frequent adverse events from the double-blind and open-label clinical trials were headache (15%), followed by dyspepsia (14%), and flu syndrome (10%). The incidence of other adverse events occurring in 3% to 9% of the patients are marked with an asterisk.

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

Incidence greater than 1% (probable causal relationship)

Body as a Whole—Pain (back)*, pain*, infection*, fever, injury (accident), asthenia, pain chest, headache (15%), flu syndrome (10%).

Gastrointestinal—Nausea*, diarrhea*, constipation*, abdominal pain*, flatulence, gastritis, vomiting, dysphagia, dyspepsia (14%), *heartburn**, *stomatitis*.

Hematologic—Anemia, ecchymosis.

Respiratory—Pharyngitis*, rhinitis*, sinusitis*, bronchitis, cough increased.

Renal—Urinary tract infection*, cystitis.

Dermatologic—Skin rash*, *skin eruptions**, *ecchymoses**, *purpura*.

Metabolic and Nutrition—Peripheral edema, hyperglycemia.

Central Nervous System—Dizziness, paresthesia, insomnia, *drowsiness**, *lightheadedness*.

Cardiovascular—Hypertension, *edema**, *dyspnea**, *palpitations*.

Musculoskeletal—Cramps (leg), myalgia, arthralgia, joint disorder, tendon disorder.

Special Senses—*Tinnitus**, *hearing disturbances*, *visual disturbances*.

General—*Thirst*.

Incidence less than 1% (probable causal relationship)

Body as a Whole—Abscess, monilia, neck rigid, pain neck, abdomen enlarged, carcinoma, cellulitis, edema general, LE syndrome, malaise, mucous membrane disorder, allergic reaction, pain pelvic.

Gastrointestinal—Anorexia, cholecystitis, cholelithiasis, eructation, GI hemorrhage, rectal hemorrhage, stomatitis aphthous, stomatitis ulcer, ulcer mouth, ulcer stomach, periodontal abscess, cardiospasm, colitis, esophagitis, gastroenteritis, GI disorder, rectal disorder, tooth disorder, hepatosplenomegaly, liver function abnormality, melena, ulcer esophagus, *hematemesis*, *jaundice*, *pancreatitis*, *necrosis*.

Renal—Dysmenorrhea, dysuria, kidney function abnormality, nocturia, prostate disorder, pyelonephritis, carcinoma breast, urinary incontinence, kidney calculus, kidney failure, menorrhagia, metrorrhagia, neoplasm breast, nephrosclerosis, hematuria, pain kidney, pyuria, urine abnormal, urinary frequency, urinary retention, uterine spasm, vaginitis, *glomerular nephritis*, *hyperkalemia*, *interstitial nephritis*, *nephrotic syndrome*, *renal disease*, *renal failure*, *renal papillary necrosis*.

Hematologic—Leukopenia, bleeding time increased, eosinophilia, abnormal RBC, abnormal WBC, thrombocytopenia, *agranulocytosis*, *granulocytopenia*.

Central Nervous System—Depression, anxiety, hypertonia, nervousness, neuralgia, neuritis, vertigo, amnesia, confusion, co-ordination, abnormal diplopia, emotional lability, hematoma subdural, paralysis, *dream abnormalities*, *inability to concentrate*, *muscle weakness*.

Dermatologic: Angiodermatitis, herpes simplex, dry skin, sweating, ulcer skin, acne, alopecia, dermatitis contact, eczema, herpes zoster, nail disorder, skin necrosis, subcutaneous nodule, pruritus, urticaria, neoplasm skin, *photosensitive dermatitis*, *photosensitivity reactions resembling porphyria cutaneous tarda*, *epidermolysis bullosa*.

Special Senses—Amblyopia, scleritis, cataract, conjunctivitis, deaf, ear disorder, keratoconjunctivitis, lacrimation disorder, otitis media, pain eye.

Cardiovascular—Angina pectoris, coronary artery disease, myocardial infarction, deep thrombophlebitis, vasodilation, vascular anomaly, arrhythmia, bundle branch block, abnormal ECG, heart failure right, hemorrhage, migraine, aortic stenosis, syncope, tachycardia, *congestive heart failure*.

Respiratory—Asthma, dyspnea, lung edema, laryngitis, lung disorder, epistaxis, pneumonia, respiratory distress, respiratory disorder, *eosinophilic pneumonitis*.

Musculoskeletal—Myasthenia, bone disorder, spontaneous bone fracture, fibrotendinitis, bone pain, ptosis, spasm general, bursitis.

Metabolic and Nutrition—Creatinine increase, glucosuria, hypercholesteremia, albuminuria, alkalosis,

BUN increased, dehydration, edema, glucose tolerance decrease, hyperuricemia, hypokalemia, SGOT increase, SGPT increase, weight decrease.

General—*Anaphylactoid reactions, angioneurotic edema, menstrual disorders, hypoglycemia, pyrexia (chills and fevers).*

Incidence less than 1% (causal relationship unknown)

Other adverse reactions listed in the naproxen package label, but not reported by those who received Naproxen Sodium Controlled-Release Tablets are shown in italics. These observations are being listed as alerting information to the physician.

Hematologic—*Aplastic anemia, hemolytic anemia.*

Central Nervous System—*Aseptic meningitis, cognitive dysfunction.*

Dermatologic—*Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.*

Gastrointestinal—*Non-peptic GI ulceration, ulcerative stomatitis.*

Cardiovascular—*Vasculitis.*

7 DRUG INTERACTIONS

See Table 1 for clinically significant drug interactions with naproxen.

Table 1: Clinically Significant Drug Interactions with Naproxen

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of naproxen sodium with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.11)*].
Aspirin	
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)*].
Intervention:	Concomitant use of naproxen sodium and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.11)*]. Naproxen sodium is 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 sodium and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of naproxen sodium 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)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
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 sodium with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of naproxen sodium and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in 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.
Intervention:	During concomitant use of naproxen sodium and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of naproxen sodium and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of naproxen sodium and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of naproxen sodium and cyclosporine, monitor patients for signs of worsening renal function.
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 with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of naproxen sodium 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 sodium and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Antacids and Sucralfate	
Clinical Impact:	Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.
Intervention:	Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with naproxen sodium is not recommended.
Cholestyramine	
Clinical Impact:	Concomitant administration of cholestyramine can delay the absorption of naproxen.
Intervention:	Concomitant administration of cholestyramine with naproxen sodium is not recommended.
Probenecid	
Clinical Impact:	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.
Intervention:	Patients simultaneously receiving naproxen sodium and probenecid should be observed for adjustment of dose if required.
Other albumin-bound drugs	
Clinical Impact:	Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin.
Intervention:	Patients simultaneously receiving naproxen sodium and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Drug/Laboratory Test Interactions

Bleeding times	
Clinical Impact:	Naproxen may decrease platelet aggregation and prolong bleeding time.
Intervention:	This effect should be kept in mind when bleeding times are determined.
Porter-Silber test	
Clinical Impact:	The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay.
Intervention:	Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen

Intervention:	sodium be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.
Urinary assays of 5-hydroxy indoleacetic acid (5HIAA)	
Clinical Impact:	Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).
Intervention:	This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid are determined.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 no adequate and well-controlled studies of naproxen sodium in pregnant women.

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters 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, rabbit, and mice no evidence of teratogenicity or fetal harm when naproxen was 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/day, respectively.
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 sodium resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of naproxen sodium during labor or delivery. In animal studies, NSAIDS, including naproxen sodium, inhibit prostaglandin synthesis, cause delayed parturition, increase incidence of dystocia and increase the incidence of stillbirth.

Data

Human Data

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor, there is an increased 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. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus), use during third trimester should be avoided.

Animal data

Reproduction studies have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1,500 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 (0.6 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of impaired fertility or harm to the fetus due to the drug. 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 sodium resulted in increased pre- and post-implantation loss.

8.2 Lactation

Risk Summary

The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for naproxen sodium and any potential adverse effects on the breastfed infant from the naproxen sodium 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 sodium, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including naproxen sodium, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

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

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, 5.13)*].

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, use caution in this patient population, and it may be useful to monitor renal function [*see Clinical Pharmacology (12.3)*]

10 OVERDOSAGE

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)*].

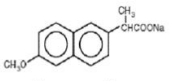
A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening.

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.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

Naproxen Sodium Controlled-Release Tablets is a nonsteroidal anti-inflammatory drug, available as controlled-release tablets in 375 mg strength for oral administration. The chemical name is 2-naphthaleneacetic acid, 6-methoxy-α-methyl-sodium salt, (S)-. The molecular weight is 252.24. Its molecular formula is $C_{14}H_{13}NaO_3$, and it has the following chemical structure.



Naproxen sodium
Molecular Formula: $C_{14}H_{13}NaO_3$ Molecular Weight: 252.24

Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water. 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 Tablet also contains the following inactive ingredients: ammoniomethacrylate copolymer Type A,

ammoniomethacrylate copolymer Type B, citric acid, crospovidone, magnesium stearate, methacrylic acid copolymer Type A, microcrystalline cellulose, povidone, and talc. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naproxen has analgesic, 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).

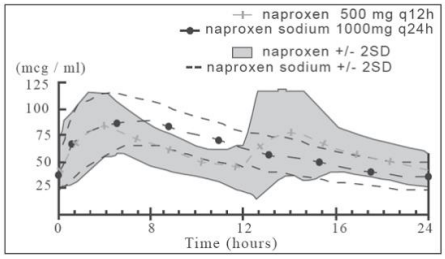
Naproxen sodium is a potent inhibitor of prostaglandin synthesis *in vitro*. Naproxen sodium concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models.

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

12.3 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 microparticles 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 (+/-2SD) (Steady State, Day 5)



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

Parameter (units)	naproxen 500 mg Q12h/5 days (1000 mg)			Naproxen Sodium Controlled-Release 2 x 500 mg tablets (1000 mg) Q24h/5 days		
	Mean	SD	Range	Mean	SD	Range
AUC 0-24 (mcgxh/mL)	1446	168	1167 - 1858	1448	145	1173 - 1774
C_{max} (mcg/mL)	95	13	71 - 117	94	13	74 - 127
C_{avg} (mcg/mL)	60	7	49 - 77	60	6	49 - 74
C_{min} (mcg/mL)	36	9	13 - 51	33	7	23 - 48
T_{max} (hrs)	3	1	1 - 4	5	2	2-10

Absorption

Naproxen itself is rapidly and completely absorbed from the GI tract with an *in vivo* 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 disintegration of the tablet in the stomach, the transit of the sustained release microparticles through the small intestine and into the proximal large intestine. An *in vivo* imaging study has been performed in healthy volunteers that confirms rapid disintegration of the tablet matrix and dispersion of the microparticles.

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 maintains 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 naproxen sodium formulations, food causes a slight decrease in the rate of naproxen absorption following Naproxen Sodium Controlled-Release Tablets administration.

Distribution

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 a less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses. However the concentration of unbound naproxen continues to increase proportionally to dose. Naproxen Sodium Controlled-Release Tablets exhibit similar dose proportional characteristics.

Elimination

Metabolism

Naproxen is extensively metabolized to 6-0-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 1%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66 to 92%). A small amount (<5%) of the drug is excreted in the feces. The rate of excretion has been found to coincide closely with 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 populations has not been established.

Hepatic Impairment:

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (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 <30mL/min) [*see Warnings and Precautions (5.6)*].

Drug Interaction Studies

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 1 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 24 mg/kg/day (0.05, 0.1, and 0.16 times the maximum recommended human daily dose of 1,500 mg/day based on a body surface area comparison). No evidence of tumorigenicity was found.

Mutagenesis

Studies to evaluate the mutagenic 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

Rheumatoid 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.

Osteoarthritis

The use of Naproxen Sodium Controlled-Release Tablets for the management of the signs and symptoms of osteoarthritis of the knee 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.

Analgesia

The onset of the analgesic effect of Naproxen Sodium Controlled-Release Tablets was seen within 30 minutes in a pharmacokinetic/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 rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs the combination may result in higher frequency of adverse events than 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. Mucosal biopsy scores and endoscopic 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 naproxen 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 tablet with “N” on one side and “375” on the reverse; in bottles of 100; NDC 69420-1375-1. 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].

PHARMACIST: Dispense in a well-closed container.

17 PATIENT COUNSELING INFORMATION

Advise 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

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 health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Naproxen sodium, like other NSAIDs, can 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 ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care 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, 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 Reactions

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, can 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 (5.9)*].

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 (8.3)*].

Fetal Toxicity

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

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant 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 little or no 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 concomitantly with naproxen sodium until they talk to their healthcare provider [*see Drug Interactions (7)*].

Manufactured for:

SA3, LLC

Los Angeles, CA 90064

PI1375-00

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)."
Avoid 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 (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

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 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 29 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

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 are 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)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness

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

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

If you take too much of your NSAID, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of 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.

Manufactured for:
SA3, 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.

PL1375-00
Rev. 04/2019

PRINCIPAL DISPLAY PANEL

NDC 69420-1375-1
Naproxen Sodium
Controlled-Release
Tablets
375 mg
Rx Only
100 Tablets

NAPROXEN SODIUM

naproxen sodium tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69420-1375
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NAPROXEN SODIUM (UNII: 9TN87S3A3C) (NAPROXEN - UNII:57Y76R9ATQ)	NAPROXEN	375 mg

Inactive Ingredients	
Ingredient Name	**Strength**
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161HDB14U2)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHWBQP)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6THI3)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
TALC (UNII: 7SEV7J4R1U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	CAPSULE	**Size**	15mm
Flavor		**Imprint Code**	N;375
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69420-1375-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/01/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA020353	05/01/2019	

Labeler - SA3, LLC (079627454)

Revised: 4/2019 SA3, LLC