NAPROXEN SODIUM - naproxen sodium tablet, film coated
A-S Medication Solutions

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

NAPROXEN SODIUM 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 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)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.10, 5.11) 04/2021

INDICATIONS AND USAGE

Naproxen sodium tablets are non-steroidal anti-inflammatory drugs indicated for: (1)

the relief of the signs and symptoms of:
- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- polyarticular juvenile idiopathic arthritis
- tendonitis
- bursitis
- acute gout

the management of:
- pain
- primary dysmenorrhea

DOSAGE AND ADMINISTRATION

Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2.1)

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

Naproxen sodium tablets	275 mg 550 mg	twice daily

The dose may be adjusted up or down depending on the clinical response of the patient. In patients who tolerate lower doses well, the dose may be increased to naproxen sodium 1650 mg (equivalent to 1500 mg naproxen) per day for up to 6 months.

Polyarticular Juvenile Idiopathic Arthritis
Naproxen tablets may not allow for the flexible dose titration needed in pediatric patients with polyarticular juvenile idiopathic arthritis. A liquid formulation may be more appropriate. Recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. Dosing with naproxen tablets is not appropriate for children weighing less than 50 kilograms.

Management of Pain, Primary Dysmenorrhea, and Acute Tendonitis and Bursitis
Recommended starting dose 550 mg of naproxen sodium as naproxen sodium tablets followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. Naproxen sodium tablets are recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

Acute Gout

Naproxen sodium tablets may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours.

DOSAGE FORMS AND STRENGTHS

Naproxen sodium tablets: 275 mg (naproxen 250 mg with 25 mg sodium)
550 mg (naproxen 500 mg with 50 mg sodium) (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 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 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 is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
Serious Skin Reactions: Discontinue naproxen sodium at first appearance of skin rash or other signs of hypersensitivity. (5.9)
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10).
Fetal Toxicity: Limit use of NSAIDs, including naproxen sodium, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus. (5.11, 8.1)
Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.12, 7)

ADVERSE REACTIONS

Most common adverse reactions to naproxen were dyspepsia, abdominal pain, nausea, headache, rash, ecchymosis, and edema. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 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 with drugs that interfere with hemostasis. Concomitant use of naproxen sodium and analgesic doses of aspirin is not generally recommended. (7)
ACE inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with naproxen sodium may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
ACE Inhibitors and ARBs: Concomitant use with naproxen sodium 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 can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)

USE IN SPECIFIC POPULATIONS

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of naproxen sodium in women who have difficulties conceiving. (8.3)
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). (8.7)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4), 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 tablets are indicated for:

the relief of the signs and symptoms of:

- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- Polyarticular Juvenile Idiopathic Arthritis
- tendonitis
- bursitis
- acute gout

the management of:

- pain
- primary dysmenorrhea

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of naproxen sodium tablets and other treatment options before deciding to use naproxen sodium tablets. Use the lowest effective dose 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 tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

Naproxen-containing products such as naproxen sodium tablets, and other naproxen products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

2.2 Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

The recommended dosages of naproxen sodium tablets are shown in Table 1.

Table 1: Recommended dosages for naproxen sodium tablets

Naproxen sodium tablets	275 mg (naproxen 250 mg with 25 mg sodium) 550 mg (naproxen 500 mg with 50 mg sodium)	twice daily

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration.

The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response.

In patients who tolerate lower doses well, the dose may be increased to naproxen sodium 1650 mg (equivalent to 1500 mg naproxen) per day for limited periods of up to 6 months when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen sodium 1650 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk.

2.3 Polyarticular Juvenile Idiopathic Arthritis

Naproxen solid-oral dosage forms may not allow for the flexible dose titration needed in pediatric patients with polyarticular juvenile idiopathic arthritis. A liquid formulation may be more appropriate for weight-based dosing and due to the need for dose flexibility in children.

In pediatric patients, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen *[see Clinical Pharmacology (12)]*. The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. Dosing with naproxen tablets is not appropriate for children weighing less than 50 kilograms.

2.4 Management of Pain, Primary Dysmenorrhea, and Acute Tendonitis and Bursitis

The recommended starting dose of naproxen sodium tablets is 550 mg followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. Because the sodium salt of naproxen is more rapidly absorbed, naproxen sodium tablets are recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

2.5 Acute Gout

Naproxen sodium tablets may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours.

2.6 Non-Interchangeability with Other Formulations of Naproxen

Different dose strengths and formulations (e.g., tablets, suspension) of naproxen are not interchangeable. This difference should be taken into consideration when changing strengths or formulations.

3 DOSAGE FORMS AND STRENGTHS

Naproxen Sodium Tablets USP, 275 mg are light blue color, oval shaped, film-coated tablets engraved with "T 21" on one side & plain on the other side.

Naproxen Sodium Tablets USP, 550 mg are dark blue color, modified capsule shaped, film-coated tablets engraved with "T & 22" on either side of scoreline on one side & with scoreline on the other side.

4 CONTRAINDICATIONS

Naproxen sodium 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 to 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 in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If naproxen sodium is 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 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 immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including naproxen sodium can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, 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 in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If naproxen sodium is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Since each naproxen sodium tablet contains 25 mg or 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), this should be considered in patients whose overall intake of sodium must be severely restricted.

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 in patients with advanced renal disease. The renal effects of naproxen sodium 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. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of naproxen sodium *[see Drug Interactions (7)]*. Avoid the use of naproxen sodium in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If naproxen sodium is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

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

5.7 Anaphylactic Reactions

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

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, naproxen sodium is contraindicated in patients with this form of aspirin

sensitivity *[see Contraindications (4)]*. When naproxen sodium is 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 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 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

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

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including naproxen sodium, in pregnant women at about 30 weeks of gestation and later. NSAIDs, including naproxen sodium, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

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

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit naproxen sodium use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if naproxen sodium treatment extends beyond 48 hours. Discontinue naproxen sodium if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)]*.

5.12 Hematologic Toxicity

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

NSAIDs, including naproxen sodium may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin and other anticoagulants, antiplatelet agents (e.g., aspirin), 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)]*.

5.13 Masking of Inflammation and Fever

The pharmacological activity of naproxen sodium in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Long-Term Use and 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)]*.

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

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

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 (5.12)]*

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.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen.

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with polyarticular juvenile idiopathic arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were greater, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

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

Gastrointestinal (GI) Experiences, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis

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

Dermatologic: pruritus (itching)*, skin eruptions*, ecchymoses*, sweating, purpura

Special Senses: tinnitus*, visual disturbances, hearing disturbances

Cardiovascular: edema*, palpitations

General: dyspnea*, thirst

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

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

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

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

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

Gastrointestinal: pancreatitis, vomiting

Hepatobiliary: jaundice

Hemic and Lymphatic: melena, thrombocytopenia, agranulocytosis

Nervous System: inability to concentrate

Dermatologic: skin rashes

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of naproxen. Because these reactions are reported voluntarily from a population of

uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through postmarketing reports are italicized.

Body as a Whole: anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)

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

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

Hepatobiliary: abnormal liver function tests, hepatitis (some cases have been fatal)

Hemic and Lymphatic: eosinophilia, leucopenia, granulocytopenia, hemolytic anemia, aplastic anemia

Metabolic and Nutritional: hyperglycemia, hypoglycemia

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

Respiratory: eosinophilic pneumonitis, asthma

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

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

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

Reproduction (female): infertility

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

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

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

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation

Hepatobiliary: hepatitis, liver failure

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis

Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with naproxen.

Table 2: 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 (5.12)]*.
Aspirin	
Clinical Impact:	A pharmacodynamic (PD) study has demonstrated an interaction in which lower dose naproxen (220 mg/day or 220 mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen [*see Clinical Pharmacodynamics (12.2)*]. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the PD study due to the longer washout period. 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:	Because there may be an increased risk of cardiovascular events following discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics where appropriate. 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 (5.12)]*. Naproxen sodium is not substitutes 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-dinitrobenzene 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 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 is determined.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including naproxen sodium, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

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

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies in rats, rabbits, 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 1500 mg/day, respectively [see *Data*]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including naproxen sodium, can cause premature closure of the fetal ductus arteriosus (see *Data*).

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If naproxen sodium treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue naproxen sodium, and follow up according to clinical practice (see *Data*).

Labor or Delivery

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

Data

Human Data

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 effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly starting at 30-weeks of gestation, or third trimester) should be avoided.

Premature Closure of Fetal Ductus Arteriosus:

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

Oligohydramnios/Neonatal Renal Impairment:

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

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

Animal data

Reproduction studies have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison), rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose, based on body surface area comparison), and mice at 170 mg/kg/day (0.6 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.

8.2 Lactation

Risk Summary

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma.

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

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for polyarticular juvenile idiopathic arthritis are based on well-controlled studies *[see Dosage and Administration (2)]*. There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in polyarticular juvenile idiopathic arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg as naproxen suspension, with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

8.5 Geriatric Use

The hepatic and renal tolerability of long-term naproxen administration was studied in two double-blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. NAPROXEN was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

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

Studies indicate that although total plasma concentration of naproxen is unchanged, the

unbound plasma fraction of naproxen is increased in the elderly. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients. 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.

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

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Clinical Pharmacology (12.3)]*. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs *[see Warnings and Precautions (5.6)]*.

8.6 Hepatic Impairment

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 *[see Clinical Pharmacology (12.3)]*.

8.7 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), 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)]*. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated.

A few patients have experienced convulsions, 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. *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)]*.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. 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 tablets, USP are nonsteroidal anti-inflammatory drugs and available as light blue color tablets containing 275 mg of naproxen sodium and dark blue color tablets containing 550 mg of naproxen sodium for oral administration.

Naproxen sodium is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs. The chemical name for naproxen sodium is (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt. Naproxen sodium has a molecular weight of 252.23 and a molecular formula of $C_{14}H_{13}NaO_3$. It has the following structural formula:

naproxen sodium (R=-COONa) $C_{14}H_{13}NaO_3$

Naproxen sodium USP is a white to creamy crystalline powder, freely soluble in water at neutral pH.

Each naproxen sodium tablet, USP contains the following inactive ingredients: colloidal silicon dioxide, FD&C Blue #2, hypromellose, magnesium stearate, microcrystalline cellulose, PEG 8000, povidone, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naproxen has analgesic, anti-inflammatory, and antipyretic properties. Naproxen sodium has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic.

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

Naproxen is a potent inhibitor of prostaglandin synthesis *in vitro*. Naproxen concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once-daily with low-dose immediate-release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 inhibition at 24 hours following the day 10 dose [98.7% (aspirin alone) vs 93.1% (naproxen and aspirin)]. The interaction was observed even following discontinuation of naproxen on day 11 (while aspirin dose was continued) but normalized by day 13. In the same study, the interaction was greater when naproxen was administered 30 minutes prior to aspirin [98.7% vs 87.7%] and minimal when aspirin was administered 30 minutes prior to naproxen [98.7% vs 95.4%].

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

12.3 Pharmacokinetics

Naproxen sodium is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. The elimination half-life of naproxen ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life.

Absorption

After oral administration of naproxen sodium tablets, peak plasma levels are attained in 1 to 2 hours.

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

Elimination

Metabolism

Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Excretion

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen clearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate *[see Warnings and Precautions (5.6)]*.

Specific Populations

Pediatric:

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension *[see Dosage and Administration (2)]* were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen tablets in pediatric patients.

Geriatric:

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects.

Hepatic Impairment:

Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

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.

Renal Impairment:

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment.

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

Mutagenesis

Naproxen tested positive in the *in vivo* sister chromatid exchange assay for but was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test).

Impairment of Fertility

Male rats were treated with 2, 5, 10, and 20 mg/kg naproxen by oral gavage for 60 days prior to mating and female rats were treated with the same doses for 14 days prior to mating and for the first 7 days of pregnancy. There were no adverse effects on fertility noted (up to 0.13 times the MRDH based on body surface area).

14 CLINICAL STUDIES

Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg twice a day (750 mg a day) vs 750 mg twice a day (1500 mg/day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and polyarticular juvenile idiopathic arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen and within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates 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.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1100 mg of naproxen sodium has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

16 HOW SUPPLIED/STORAGE AND HANDLING

Product: 50090-3352

NDC: 50090-3352-3 20 TABLET, FILM COATED in a BOTTLE

NDC: 50090-3352-5 30 TABLET, FILM COATED in a BOTTLE

NDC: 50090-3352-6 60 TABLET, FILM COATED in a BOTTLE

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 tablets 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

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 tablets and seek immediate medical therapy *[see Warnings and Precautions (5.3)]*.

Heart Failure and Edema

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

Anaphylactic Reactions

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

Serious Skin Reactions, including DRESS

Advise patients to stop taking naproxen sodium tablets immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.9, 5.10)]*.

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including naproxen sodium tablets, 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 tablets and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with naproxen sodium is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of naproxen sodium tablets with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy *[see Warnings and Precautions (5.2)* 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 tablets until they talk to their healthcare provider *[see Drug Interactions (7)]*.

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www.aurobindousa.com/medication-guides

Distributed by:
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Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 032, India

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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. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare prounder may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 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.

For more information, call Aurobindo Pharma USA, Inc. at 1-866-850-2876.

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Revised: 05/2021

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

Naproxen Sodium

NAPROXEN SODIUM
naproxen sodium tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50090-3352(NDC:65862-516)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NAPROXEN SODIUM (UNII: 9TN87S3A3C) (NAPROXEN - UNII:57Y76R9ATQ)	NAPROXEN SODIUM	550 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
POVIDONE K30 (UNII: U725QWY32X)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	BLUE (Dark Blue)	**Score**	2 pieces
Shape	CAPSULE (Modified Capsule Shaped)	**Size**	19mm
Flavor		**Imprint Code**	T;22
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:50090-3352-3	20 in 1 BOTTLE; Type 0: Not a Combination Product	01/29/2018	
2	NDC:50090-3352-5	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/12/2018	
3	NDC:50090-3352-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	07/12/2018	

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA200629	10/31/2011	

Labeler - A-S Medication Solutions (830016429)

Establishment			
Name	**Address**	**ID/FEI**	**Business Operations**
A-S Medication Solutions		830016429	RELABEL(50090-3352) , REPACK(50090-3352)