

**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
These highlights do not include all the information needed to use NAPRELAN® safely and effectively. See full prescribing information for NAPRELAN®.

**NAPRELAN (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)**
- **NAPRELAN is 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

NAPRELAN 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

NAPRELAN (naproxen sodium) Controlled-Release Tablets: 375 mg, 500 mg, and 750 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 NAPRELAN 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 NAPRELAN 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:** NAPRELAN is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- **Serious Skin Reactions:** Discontinue NAPRELAN 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 NAPRELAN, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1).
- **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

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

**REPORT SUSPECTED ADVERSE REACTIONS, contact Almatica Pharma LLC at 1-877-447-7979 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 NAPRELAN with drugs that interfere with hemostasis. Concomitant use of NAPRELAN and analgesic doses of aspirin is not generally recommended (7)

**ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers:** Concomitant use with NAPRELAN may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

**ACE Inhibitors and ARBs:** Concomitant use with NAPRELAN 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 NAPRELAN can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

**Infertility:** NSAIDs are associated with reversible infertility. Consider withdrawal of NAPRELAN in women who have difficulties conceiving (8.3)

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## DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of NAPRELAN and other treatment options before deciding to use NAPRELAN. 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 NAPRELAN, 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 NAPRELAN Tablets in adults is two NAPRELAN 375 mg tablets (750 mg) once daily, one NAPRELAN 750 mg (750 mg) once daily, or two NAPRELAN 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 NAPRELAN Tablets as a single daily dose.

During long-term administration, the dose of NAPRELAN Tablets may be adjusted up or down depending on the clinical response of the patient. In patients who tolerate lower doses of NAPRELAN Tablets well, the dose may be increased to two NAPRELAN 750 mg tablets (1,500 mg), or three NAPRELAN 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 of NAPRELAN 500 mg tablets (1,000 mg) once daily. For patients requiring greater analgesic benefit, two NAPRELAN 750 mg tablets (1,500 mg) or three NAPRELAN 500 mg tablets (1,500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two NAPRELAN 500 mg tablets (1,000 mg).

### 2.4 Acute Gout

The recommended dose on the first day is two to three NAPRELAN 500 mg tablets (1,000 to 1,500 mg) once daily, followed by two NAPRELAN 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

NAPRELAN (naproxen sodium) Controlled-Release Tablets are available as follows:

**NAPRELAN 375:** 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.

**NAPRELAN 500:** white, capsule-shaped tablet with "N" on one side and "500" on the reverse. Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

**NAPRELAN 750:** white, capsule-shaped tablet with "N" on one side and "750" on the reverse. Each tablet contains 825 mg naproxen sodium equivalent to 750 mg naproxen.

## 4 CONTRAINDICATIONS

NAPRELAN is 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* (5.12)]

## 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 whether 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 NAPRELAN in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If NAPRELAN 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 upper 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 of GI bleeding.

### Strategies to Minimize the GI Risks in NSAID-Treated Patients

- Use the lowest effective dose 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 NAPRELAN 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 NAPRELAN immediately, and perform a clinical evaluation of the patient.

### 5.4 Hypertension

NSAIDs, including NAPRELAN, 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 responses 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 NAPRELAN in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If NAPRELAN 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 NAPRELAN in patients with advanced renal disease. The renal effects of naproxen may hasten the progression of renal dysfunction in patients with preexisting renal disease.</

**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.

**Distributed by:**

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Morristown, NJ 07960 USA

For more information, call 1-877-447-7979

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<b>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers</b>	
<i>Clinical Impact:</i>	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).
<i>Intervention:</i>	• 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. • During concomitant use of NAPRELAN and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of NAPRELAN 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 <i>Warnings and Precautions</i> (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.
<b>Diuretics</b>	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	During concomitant use of NAPRELAN with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see <i>Warnings and Precautions</i> (5.6)].
<b>Digoxin</b>	
<i>Clinical Impact:</i>	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
<i>Intervention:</i>	During concomitant use of NAPRELAN and digoxin, monitor serum digoxin levels.
<b>Lithium</b>	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	During concomitant use of NAPRELAN and lithium, monitor patients for signs of lithium toxicity.
<b>Methotrexate</b>	
<i>Clinical Impact:</i>	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
<i>Intervention:</i>	During concomitant use of NAPRELAN and methotrexate, monitor patients for methotrexate toxicity.
<b>Cyclosporine</b>	
<i>Clinical Impact:</i>	Concomitant use of NAPRELAN and cyclosporine may increase cyclosporine's nephrotoxicity.
<i>Intervention:</i>	During concomitant use of NAPRELAN and cyclosporine, monitor patients for signs of worsening renal function.
<b>NSAIDs and Salicylates</b>	
<i>Clinical Impact:</i>	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 <i>Warnings and Precautions</i> (5.2)].
<i>Intervention:</i>	The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.
<b>Pemetrexed</b>	
<i>Clinical Impact:</i>	Concomitant use of NAPRELAN and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
<i>Intervention:</i>	During concomitant use of NAPRELAN 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.
<b>Antacids and Sucralfate</b>	
<i>Clinical Impact:</i>	Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.
<i>Intervention:</i>	Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with NAPRELAN is not recommended.
<b>Cholestyramine</b>	
<i>Clinical Impact:</i>	Concomitant administration of cholestyramine can delay the absorption of naproxen.
<i>Intervention:</i>	Concomitant administration of cholestyramine with NAPRELAN is not recommended.
<b>Probenecid</b>	
<i>Clinical Impact:</i>	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.
<i>Intervention:</i>	Patients simultaneously receiving NAPRELAN and probenecid should be observed for adjustment of dose if required.
<b>Other albumin-bound drugs</b>	
<i>Clinical Impact:</i>	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, hydantoin, other NSAIDs, and aspirin.
<i>Intervention:</i>	Patients simultaneously receiving NAPRELAN and a hydantoin, sulphonyamide 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 NAPRELAN 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 (SHIAA)**

*Clinical Impact:* Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (SHIAA).

*Intervention:* This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid are determined.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Use of NSAIDs, including NAPRELAN, 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 NAPRELAN use between about 20 and 30 weeks of gestation, and avoid NAPRELAN 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 NAPRELAN, 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, 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, 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 NAPRELAN, 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 NAPRELAN treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue NAPRELAN and follow up according to clinical practice (see *Data*).

**Labor or Delivery**

There are no studies on the effects of NAPRELAN 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.

**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 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 NAPRELAN and any potential adverse effects on the breastfed infant from the NAPRELAN 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 NAPRELAN, may affect 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 NAPRELAN, in women who have difficulties conceiving or who are undergoing investigation of infertility.

**8.4 Pediatric Use**

The safety and effectiveness of NAPRELAN 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 depression, and coma have occurred, but were rare [see *Warnings and Precautions* (5.1, 5.2, 5.3, 5.6, 5.14)].

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)].

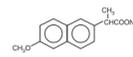
A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening.

Manage patients with symptomatic and supportive care following an NSAID overdose. 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 overdose (5 to 10 times the recommended dosage). Forced diuresis, alkalization 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**

NAPRELAN (naproxen sodium) Controlled-Release Tablets is a nonsteroidal anti-inflammatory drug, available as controlled-release tablets in 375 mg, 500 mg, and 750 mg strengths for oral administration. The chemical name is 2-naphthaleneacetic acid, 6-methoxy- $\alpha$ -methyl-sodium salt, (-). The molecular weight is 252.24. Its molecular formula is  $C_{16}H_{13}NaO_3$ , and it has the following chemical structure.



Naproxen sodium  
Molecular Formula:  $C_{16}H_{13}NaO_3$  Molecular Weight: 252.24

Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water. NAPRELAN Tablets contain 412.5 mg, 550 mg, or 825 mg of naproxen sodium, equivalent to 375 mg, 500 mg, and 750 mg of naproxen, and 37.5 mg, 50 mg, and 75 mg sodium respectively. Each NAPRELAN Tablet also contains the following inactive ingredients: ammoniummethacrylate copolymer Type A, ammoniummethacrylate copolymer Type B, citric acid, croscopolone, 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 NAPRELAN, 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 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.

**12.2 Pharmacodynamics**

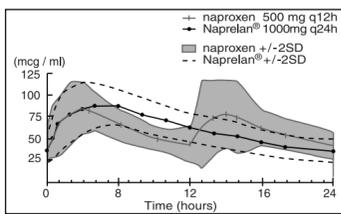
In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once-daily with low-dose immediate-release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B<sub>2</sub> inhibition at 24 hours following the day 10 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**

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 dose in NAPRELAN 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 NAPRELAN 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)			NAPRELAN 2 x 500 mg tablets (1000 mg) Q24h/5 days		
	Mean	SD	Range	Mean	SD	Range
AUC <sub>0-24</sub> (mcg·h/mL)	1446	168	1167 - 1858	1448	145	1173 - 1774
C <sub>0</sub> (mcg/mL)	95	13	71 - 117	94	13	74 - 127
C <sub>12</sub> (mcg/mL)	60	7	49 - 77	60	6	49 - 74
C <sub>24</sub> (mcg/mL)	36	9	13 - 51	33	7	23 - 48
T <sub>1/2</sub> (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 NAPRELAN Tablets occurs in the first 4 to 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 NAPRELAN 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 NAPRELAN 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 NAPRELAN 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. NAPRELAN Tablets exhibit similar dose proportional characteristics.

**Elimination**

**Metabolism**

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

**Excretion**

The elimination half-life of NAPRELAN Tablets and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2 to 3 doses of NAPRELAN Tablets. Most of the drug is excreted in the urine primarily as unchanged naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (86 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 NAPRELAN Tablets, thus safety of NAPRELAN 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 NAPRELAN 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 NAPRELAN 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 NAPRELAN 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 NAPRELAN 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 NAPRELAN 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 increased 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 NAPRELAN 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 NAPRELAN Tablets. In