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. anti-inflammatory drugs Nonsteroidal
- (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 spondýlitís (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-

Kino xA

PKG03058 Rev. 04/2023

NAPRELAN®

PKG03058 Rev. 04/2023

Rx only

NAJARAAN

- 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)
- FULL PRESCRIBING INFORMATION: CONTENTS' WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
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- 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
 the 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)].
- NAPRELAN is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4) and Warnings and Precautions (5.1)]
- Gastrointestinal Bleeding, Ulceration, and Perforation
 NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation to 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)].
- INDICATIONS AND USAGE
- NAPRELAN Tablets are indicated for the treatment of: rheumatoid arthritis (RA)
- osteoarthritis (OA)
- ankylosing spondylitis (AS)
 tendinitis, bursitis
- acute gout
- primary dysmenorrhea (PD)
 the relief of mild to moderate pair
- [see Warnings and Precautions (5)].

- <u>Hypertension</u>: 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 2.2 Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis 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)
- <u>Anaphylactic Reactions</u>: Seek emergency help if an 2.3 anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: NAPRELAN is contraindicated in patients with aspirin-sensitive asthma. Monitor
- sensitivity) (5.8) Serious Skin Reactions: Discontinue NAPRELAN
- hypersensitivity (5.9) Drug Reaction with Eosinophilia and Systemic
- clinically (5.10).
- NAPRELAN, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal NAPRELAN 500: white, capsule-shaped tablet with "N" on one side and "500" on the reverse. Each tablet contains 550 mg naproxen sodium renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy NAPRELAN 750: white, capsule-shaped tablet with "N" on one side and "750" on the reverse. Each tablet contains 825 mg naproxen sodium due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal 4 ductus arteriosus (5.11, 8.1).
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic of anemia (5.12.7)

-----ADVERSE REACTIONS------

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

To report SUSPECTED ADVERSE REACTIONS, contact Almatica Pharma LLC at 1-877-447-7979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--DRUG INTERACTIONS-- <u>Drugs that Interfere with Hemostasis (e.g.</u> warfarin, <u>aspirin</u>, <u>SSRIs/SNRIs</u>): 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) <u>ACE Inhibitors and ARBs</u>: 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) -- USE IN SPECIFIC POPULATIONS--

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2023

5.11 Fetal Toxicity

- 5.12 Hematologic Toxicity 5.13 Masking of Inflammation and Fever
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*Sections or subsections omitted from the full Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In prescribing information are not listed.

Management of Pain, Primary Dysmenorrhea, and Acute Tendinitis and Bursitis The recommended starting dose is two 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).

DOSAGE AND ADMINISTRATION

Dosage Adjustments in Patients with Hepatic Impairmen

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

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)]

the elderly it is prudent to use the lowest effective dose.

DOSAGE FORMS AND STRENGTHS

equivalent to 375 mg naproxen

equivalent to 500 mg naproxen

equivalent to 750 mg naproxe

Precautions (5.2)

Post-MI Patients

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CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

CV thrombotic risk has been observed most consistently at higher doses.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Gastrointestinal Bleeding, Ulceration, and Perforation

Risk Factors for GI Bleeding, Ulceration, and Perforation

Strategies to Minimize the GI Risks in NSAID-treated patients:

vent is ruled out

Drug Interactions (7)].

5.6 Renal Toxicity and Hyperkalemia

Hyperkalemia

5.7 Anaphylactic Reactions

5.9 Serious Skin Reactions

is usually followed by recovery to the pretreatment state.

Seek emergency help if an anaphylactic reaction occurs

changes in the signs and symptoms of asthma.

have been reported.

Use the lowest effective dosage for the shortest possible duration. Avoid administration of more than one NSAID at a time.

with active GI bleeding, consider alternate therapies other than NSAIDs.

Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy

arefully consider the potential benefits and risks of NAPRELAN and other treatment options before deciding to use NAPRELAN. Use the lowest

After observing the response to initial therapy with NAPRELAN, the dose and frequency should be adjusted to suit an individual patient's needs.

The recommended starting dose of NAPRELAN Tablets in adults is two NAPRELAN 375 mg tablets (750 mg) once daily, one NAPRELAN 750 mg

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 Tables well, the dose may be increased to two NAPRELAN 750 mg tables (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

ment in arthritis usually begins within one week; however, treatment for two weeks may be required to achieve a therapeutic benefit.

he 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

A lower does 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

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

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)]

5.1 Cardiovascular Thrombolic 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

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

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

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

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

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.

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

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

If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue NAPRELAN until a serious GI adverse

• In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see

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

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 response to these therapies when taking NSAIDs [see Drug Interactions (7)].

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

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of

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

these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglanding 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

No information is available from controlled clinical studies regarding the use of NAPRELAN in patients with advanced renal disease. The renal effects of NAPRELAN may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating NAPRELAN. Monitor renal function in patients with renal or hepatie

impairment, heart failure, dehydration, or hypovolenic patients prior to initiating WAP RECAN [see Drug Interactions (7)]. Avoid the use of NAPRELAN in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If NAPRELAN is used in

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.

Naproxen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to naproxen and in patients with

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, NAPRELAN is contraindicated in patients with this form of aspirin sensitivity

[see Contraindications (4)]. When NAPRELAN is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for

NSAIDs, including naproxen can cause serious skin adverse reactions such as exfoliative dermatitis. Stevens-Johnson Svndrome (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 NAPRELAN at the first appearance of skin rash or any other sign of hypersensitivity.

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

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

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

NAPRELAN is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

patients with advanced renal disease, monitor patients for signs of worsening renal function.

aspirin-sensitive asthma [see Contraindications (4) and Warnings and Precautions (5.8)].

in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure

6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

atic, Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to

previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)]

ffective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

(750 mg) once daily, or two NAPRELAN 500 mg tablets (1,000 mg) once daily. Patients already taking naproxen 250 n daily (morning and evening) may have their total daily dose replaced with NAPRELAN Tablets as a single daily dose.

General Dosing Instructions

- 2.4 Acute Gout patients with preexisting asthma (without aspirin 500 mg tablets (1,000 mg) once daily, until the attack has subsided.
- at first appearance of skin rash or other signs of
- Symptoms (DRESS): Discontinue and evaluate 3
- Toxicity: Limit use of NSAIDs, including

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 NAPRELAN. 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 NAPRELAN and evaluate

the patient immediately

5.11 Fetal Toxicity

were required.

infections.

stomatitis

General—Thirst.

granulocytopenia.

heart failure.

pneumoniti

Clinical Impact:

Aspirin

Interventi

xen 250 mg, 375 mg, or 500 mg twice

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

<u>Oligohydramnios/Neonatal Renal Impairment</u> Use of NSAIDs, including NAPRELAN, 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 weer renuired

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit NAPRELAN use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NAPRELAN treatment extends beyond 48 hours. Discontinue NAPRELAN 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 NAPRELAN has any signs or symptoms of anemia, monitor hemoglobin or hematocrit. NSAIDs, including NAPRELAN, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use

of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)]. 5.13 Masking of Inflammation and Fever

The pharmacological activity of NAPRELAN in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting

5.14 Laboratory Monitoring

toxicity, and renal injury can occur without warning symptoms or signs, c Because serious GI bleeding, h der monitoring patients on longterm NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

ADVERSE REACTIONS ADVERSE REACTIONS Ollowing 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 (5.7)] Serious Skin Beactions [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.

As with all drugs in this class, the frequency and severity of adverse events depends on several factors: the dose of the drug and duration of treatment; the age, the sex, physical condition of the patient; any concurrent medical diagnoses or individual risk factors. The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between drug usage and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least one case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event. The adverse reactions reported were based the evidence to suggest that there is a causal relationship between drug usage and the epidence event. The adverse reactions reported were based on the results from two double-blind controlled clinical trials of three months duration with an additional nine month open-label extension. A total of 542 patients received NAPRELAN Tablets either in the double-blind period or in the nine month open-label extension. A total 232 received NAPRELAN Tablets, 167 were initially treated with Naprosyn[®] and 143 were initially treated with placebo. Adverse reactions reported by patients who received NAPRELAN Tablets are shown by body system. Those adverse reactions observed with naproxen but not reported in controlled trials with NAPRELAN Tablets are *italicized*.

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

Incidence greater than 1% (probable causal relationship

Body as a Whole—Pain (back)*, pain*, infection*, fever, injury (accident), asthenia, pain chest, headache (15%), flu syndrome (10%). Gastrointestinal-Nausea*, diarrhea*, constipation*, abdominal pain*, flatulence, gastritis, vomiting, dysphagia, dyspepsia (14%), heartburn

Hematologic—Anemia, ecchymosis

Respiratory-Pharyngitis*, rhinitis*, sinusitis*, bronchitis, cough increased

Renal-Urinary tract infection*, cystitis.

Dermatologic-Skin rash*, skin eruptions*, ecchymoses*, purpura

Metabolic and Nutrition—Perinheral edema hyperglycemia

NSAIDs, including naproventation 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

Musculoskeletal-Cramps (leg), myalgia, arthralgia, joint disorder, tendon disorder

Special Senses-Tinnitus*, hearing disturbances, visual disturbances

Incidence less than 1% (probable causal relationship)

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

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

- Renal—Dysmenorrhea, dysuria, kidney function abnormality, nocturia, prostate disorder, pyelonephritis, carcinoma breast, urinary incontinence, kidney calculus, kidney failure, menorrhagia, metrorrhagia, neoplasm breast, nephrosclerosis, hematuria, pain kidney, pyuria, urine abnormal, urinary frequency, urinary retention, uterine spasm, vaginitis, glomerular nephritis, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.
- Hematologic—Leukopenia, bleeding time increased, eosinophilia, abnormal RBC, abnormal WBC, thrombocytopenia, agranulocytosis,
- Central Nervous System—Depression, anxiety, hypertonia, nervousness, neuralgia, neuritis, vertigo, amnesia, confusion, co-ordination, abnormal diplopia, emotional lability, hematoma subdural, paralysis, dream abnormalities, inability to concentrate, muscle weakness.
- Dermatologic: Angiodermatitis, herpes simplex, dry skin, sweating, ulcer skin, acne, alopecia, dermatitis contact, eczema, herpes zoster, nail disorder, skin necrosis, subcutaneous nodule, pruritus, urticaria, neoplasm skin, photosensitive dermatitis, photosensitivity reactions resemblin, porphyria cutaneous tarda, epidermolysis bullosa
- Special Senses—Amblyopia, scleritis, cataract, conjunctivitis, deaf, ear disorder, keratoconjunctivitis, lacrimation disorder, otitis media, pain eye. Cardiovascular—Angina pectoris, coronary artery disease, myocardial infarction, deep thrombophlebitis, vasodilation, vascular anomaly, arrhythmia, bundle branch block, abnormal ECG, heart failure right, hemorrhage, migraine, aortic stenosis, syncope, tachycardia, *congestive*
- Respiratory-Asthma, dyspnea, lung edema, laryngitis, lung disorder, epistaxis, pneumonia, respiratory distress, respiratory disorder, eosi/
- Musculoskeletal—Myasthenia, bone disorder, spontaneous bone fracture, fibrotendinitis, bone pain, ptosis, spasm general, bursitis Metabolic and Nutrition—Creatinine increase, glucosuria, hypercholesteremia, albuminuria, alkalosis, BUN increased, dehydration, edema, glucose tolerance decrease, hyperuricemia, hypokalemia, SGOT increase, SGPT increase, weight decrease.
- General-Anaphylactoid reactions, angioneurotic edema, menstrual disorders, hypoglycemia, pyrexia (chills and fevers) Incidence less than 1% (causal relationshin unknown)
- Other adverse reactions listed in the naproxen package label, but not reported by those who received NAPRELAN Tablets are shown in italics. These observations are being listed as alerting information to the physician.
- several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Hematologic—Aplastic anemia, hemolytic anemia. Drug Interactions (7)]. Central Nervous System—Aseptic meninaitis, cognitive dysfunction

 - Dermatologic—Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome. Gastrointestinal-Non-peptic GI ulceration, ulcerative stomatitis.

Cardiovascular-Vasculitis

DRUG INTERACTIONS

See Table 1 for clinically significant drug interactions with naproxer Table 1: Clinically Significant Drug Interactions with Naproxen

Drugs That Interfere with Hemostasis

- 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. Monitor patients with concomitant use of NAPRELAN 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)].
- linical Impact: A pharmacodynamic (PD) study has demonstrated an interaction in which lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen [see Clinical Pharmacology (12.2)]. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the PD study due to the longer washout period.
 - Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see Warnings and Precautions (5.2)].
 - : Because there may be an increased risk of cardiovascular events following discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patient taking low-does aspirin for cardio protection 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 NAPRELAN and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see Warnings and Precautions (5.12)]. NAPRELAN is not a substitute for low dose aspirin for cardiovascular protection.

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", 0
- "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs 0
- longer use of NSAIDs 0
- smoking 0
- drinking alcohol 0
- older age 0
- poor health 0
- advanced liver disease 0
- bleeding problems 0

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

to your healthcare provider first.

Drugs (NSAIDs)?

heart failure

and dizziness.

slurred speech

chest pain

symptoms:

- 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 provider 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.

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

See "What is the most important information I should know

about medicines called Nonsteroidal Anti-inflammatory

Other side effects of NSAIDs include: stomach pain,

constipation, diarrhea, gas, heartburn, nausea, vomiting

Get emergency help right away if you get any of the following

are breastfeeding or plan to breast feed.

What are the possible side effects of NSAIDs?

new or worse high blood pressure

liver problems including liver failure

low red blood cells (anemia)

life-threatening skin reactions

swelling of the face or throat

life-threatening allergic reactions

kidney problems including kidney failure

shortness of breath or trouble breathing

weakness in one part or side of your body

NSAIDs can cause serious side effects, including:

	÷.		
Stop taking your NSAID and call your healthcare provider	X	ACE Inhibitors, I Clinical Impact:	Angiotensin Receptor Blockers, and Beta-Blockers NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor
right away if you get any of the following symptoms:	ⁿ	onnoa mpace.	blockers (ARBs), or beta-blockers (including propranolol).
nauseamore tired or weaker than usual	1		 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.
diarrhea	i	Intervention:	 During concomitant use of NAPRELAN and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.
• itching	-		 During concomitant use of NAPRELAN and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have
your skin or eyes look yellow	i		impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)].
indigestion or stomach pain	-		 When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
flu-like symptoms	÷	Diuretics	
 vomit blood there is blood in your bowel movement or it is black and sticky like tar 	1 1 1	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 rena prostaglandin synthesis.
 unusual weight gain skin rash or blisters with fever 	 	Intervention: Digoxin	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 Warnings and Precautions (5.6)].
 swelling of the arms, legs, hands and feet 		Clinical Impact:	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life
If you take too much of your NSAID, call your healthcare		Intervention:	of digoxin. During concomitant use of NAPRELAN and digoxin, monitor serum digoxin levels.
provider or get medical help right away.		Lithium	
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about		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.
NSAIDs.	÷	Intervention:	During concomitant use of NAPRELAN and lithium, monitor patients for signs of lithium toxicity.
Call your doctor for medical advice about side	-	Methotrexate Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia
effects. You may report side effects to FDA at	÷		thrombocytopenia, renal dysfunction).
1-800-FDA-1088.	1	Intervention: Cyclosporine	During concomitant use of NAPRELAN and methotrexate, monitor patients for methotrexate toxicity.
Other information about NSAIDs	÷	Clinical Impact:	Concomitant use of NAPRELAN and cyclosporine may increase cyclosporine's nephrotoxicity.
• Aspirin is an NSAID but it does not increase the chance	1	Intervention:	During concomitant use of NAPRELAN and cyclosporine, monitor patients for signs of worsening renal function.
of a heart attack. Aspirin can cause bleeding in the brain,	÷	NSAIDs and Sali	icylates
stomach, and intestines. Aspirin can also cause ulcers in	1	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)].
the stomach and intestines.	÷	Intervention:	The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.
• Some NSAIDs are sold in lower doses without a		Pemetrexed	
prescription (over-the-counter). Talk to your healthcare	÷	Clinical Impact:	Concomitant use of NAPRELAN and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal and GI toxicity (see the pemetrexed prescribing information).
provider before using over-the-counter NSAIDs for more than 10 days.	1	Intervention:	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
5	Т		the day of, and two days following administration of pemetrexed.
General information about the safe and effective use of NSAIDs	 		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.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a		Antacids and Su	cralfate Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the
condition for which it was not prescribed. Do not give NSAIDS	I.		absorption of naproxen.
to other people, even if they have the same symptoms that you have. It may harm them.	1	Intervention: Cholestyramine	Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with NAPRELAN is not recommended.
If you would like more information about NSAIDs, talk with your	-		Concomitant administration of cholestyramine can delay the absorption of naproxen.
healthcare provider. You can ask your pharmacist or healthcare	÷.	Intervention: Probenecid	Concomitant administration of cholestyramine with NAPRELAN is not recommended.
provider for information about NSAIDs that is written for health	-		Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.
professionals.	÷	Intervention:	Patients simultaneously receiving NAPRELAN and probenecid should be observed for adjustment of dose if required.
·	-	Other albumin-b	Jound drugs Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs
Distributed by:	÷	Internetions	such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin.
Almatica Pharma LLC	-	Intervention:	Patients simultaneously receiving NAPRELAN and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.
Morristown, NJ 07960 USA	÷	Drug/Laboratory	Test Interactions
For more information, call 1-877-447-7979	-	Bleeding times	
This Medication Guide has been approved by the U.S. Food and	i	· · ·	Naproxen may decrease platelet aggregation and prolong bleeding time.
Drug Administration.	-	Intervention: Porter-Silber tes	This effect should be kept in mind when bleeding times are determined.
PL272-09	i		The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction
PL272-09 PKG03059 Rev. 04/2023		Intervention:	between the drug and/or its metabolites with m-di-nitrobenzene used in this assay.
		Urinary assays o	oliber test is to be used. of 5-hydroxy indoleacetic acid (5HIAA)

 \otimes

	 When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at th 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 rena prostaglandin synthesis.						
Intervention:	During concomitant use of NAPRELAN with diuretics, observe patients for signs of worsening renal function, in addition 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-lif of digoxin.						
Intervention:	During concomitant use of NAPRELAN 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 attribute to NSAID inhibition of renal prostaglandin synthesis.						
Intervention:	During concomitant use of NAPRELAN 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 NAPRELAN and methotrexate, monitor patients for methotrexate toxicity.						
Cyclosporine							
Clinical Impact:	Concomitant use of NAPRELAN and cyclosporine may increase cyclosporine's nephrotoxicity.						
Intervention:	During concomitant use of NAPRELAN and cyclosporine, monitor patients for signs of worsening renal function.						
NSAIDs and Sali	cvlates						
Clinical Impact:	Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, wit 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 NAPRELAN and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, rena						
	and GI toxicity (see the pemetrexed prescribing information).						
Intervention:	During concomitant use of NAPRELAN and pemetrexed, in patients with renal impairment whose creatinine clearance range 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., meloxicarr nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two day following pemetrexed administration.						
Antacids and Su	cralfate						
Clinical Impact:	Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay th absorption of naproxen.						
Intervention:	Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with NAPRELAI is not recommended.						
Cholestyramine							
	Concomitant administration of cholestyramine can delay the absorption of naproxen.						
Intervention:	Concomitant administration of cholestyramine with NAPRELAN is not recommended.						
Probenecid							
	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.						
Intervention: Other albumin-b	Patients simultaneously receiving NAPRELAN and probenecid should be observed for adjustment of dose if required.						
Clinical Impact:							
Intervention:	Patients simultaneously receiving NAPRELAN and a hydantoin, sulphonamide or sulphonylurea should be observed fo adjustment of dose if required.						
Drug/Laboratory 1	Test Interactions						
Bleeding times							
-	Naproxen may decrease platelet aggregation and prolong bleeding time.						
Intervention:	This effect should be kept in mind when bleeding times are determined.						
Porter-Silber tes							
Olinical Impost	The administration of approximation and approximation interaction during a second during the second se						

ter-Silber tes					
nical 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.				
nary assays of 5-hydroxy indoleacetic acid (5HIAA)					
nical Impact:	Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).				

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary Use of NSAIDs, including NAPRELAN, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to Use of NSAIDs, including NAPRELAN, can cause premature closure of these risks limit does and duration of NAPRELAN use between about oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of NAPRELAN use betwee 20 and 30 weeks of gestation, and avoid NAPRELAN use at about 30 weeks of gestation and later in pregnancy (see Clinical Consideration tions 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

os/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 impai 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 dosee. 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

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including NAPRELAN premature closure of the fetal ductus arteriosus (see Data

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)

There are no studies on the effects of NAPRELAN during labor or delivery. In animal studies, NSAIDS, including naproxen sodium, inhibit idin 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 neoratal complications such as necrotizing entercocitis, patent ductus arteriosus, and intracraila 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 detricing).

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 Benal Impairment

Unigonydramnios/weonatal Renai 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

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 (0.61 times the maximum recommended human daily dose on body 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.



<u>Risk Summary</u> 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

Carcinogenesis (0.0.5, 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 Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including NAPRELAN, may delay or prevent rupture of ovarian based on the mean soft action, the use of plostagatamenterological tools of the soft and the soft of t of tumorigenicity was found. Studies to evaluate the mutagenic potential of Naprosyn Suspension have not been completed

8.4 Pediatric Use tiveness 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 14

adverse reactions. If the anticipated benefit for the idderly patient outweights 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]]. The use of NAPRELAN Tablets for the management of the signs and symptoms of rheumatoid arthritis was assessed in a 12 week double-blind, mized, placebo, and active-controlled study in 348 patients. Two NAPRELAN 500 mg tablets (1,000 mg) once daily and naproxen 500 mg 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 tablets twice daily (1,000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the 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)]. duration of the study mus following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, 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-

10 OVERDOSAGE

which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)]. A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening

The onset of the analoesic effect of NAPRELAN Tablets was seen within 30 minutes in a pharmacokinetic/pharmacodynamic study of patients Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Hemodialysis does not with pain following oral surgery. In controlled clinical trials, naproxen has been used in combination with pain following oral surgery. In controlled clinical trials, naproxen has been used in combination with pain (d). D-peniciallamine, methotrexate, and corticosteroids. Its use in combination with salicylate is not recommended because there is evidence that aspirin increases the rate of excretion of decrease the plasma concentration of naproxen because of the high degree of its protein binding. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding. 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. For additional information about overdosage treatment contact a poison control center (1-800-222-1222). 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 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- α -methyl-sodium salt, (S)-. The molecular weight is 252.24. Its molecular formula is C₁₄H₁₃NaO₃, and it has the following chemical structure. MAPRELAN Tablets. In another double-blind, randomized, crossover study, 23 subjects received two NAPRELAN 500 mg tablets (1,000 mg) twice daily and aspirin 650 mg four times daily (2,600 mg) for 7 days each. There were significantly fewer duodenal erosions seen with NAPRELAN Tablets than with either naproxen or aspirin. There were significantly fewer gastric erosions with both NAPRELAN Tablets and naproxen than with aspirin. The clinical significance of these findings is unknown.

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

NAPRELAN 500: white, capsule-shaped tablet with "N" on one side and "500" on the reverse; in bottles of 75; NDC 52427-273-75. Each tablet Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water. NAPRELAN Tablets contai contains 550 mg naproxen sodium equivalent to 500 mg naproxe 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: ammoniomethacrylate copolymer Type B, citric acid, crospovidone, magnesium stearate, methacrylic acid copolymer Type A, microcrystalline NAPRELAN 750: white, capsule-shaped tablet with "N" on one side and "750" on the reverse; in bottles of 30; NDC 52427-274-30. Each tablet contains 825 mg naproxen sodium equivalent to 750 mg naproxe cellulose, povidone, and talc. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxid

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

Naproxen has analoesic, 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 inducing pain in animal m Prostaglandins are mediators of inflammation. Because naproxen sodium is an inhibitor of prostaglandin synthesis, its mode of action may be due

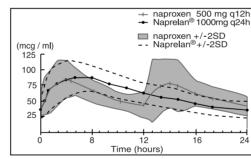
Cardiovascular Thrombotic Events to a decrease of prostaglandins in peripheral tissues. Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see Warnings and Precautions (5.1)]. 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 Gastrointestinal Bleeding, Ulceration, and Perforation (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B, 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 NAPRELAN, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)]. istered 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* 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 NAPRELAN and seek immediate medical therapy [see Warnings and Precautions (5.3)]. 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 sodium 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)	a	N		
	Mean	SD	Range	Mean
AUC 0-24 (mcgxh/mL)	1446	168	1167 - 1858	1448
C _{max} (mcg/mL)	95	13	71 - 117	94
C _{avg} (mcg/mL)	60	7	49 - 77	60
C _{min} (mcg/mL)	36	9	13 - 51	33
T _{max} (hrs)	3	1	1 - 4	5

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 table 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

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.

oxen 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 cleanance caused by saturation of plasm protein binding at higher doses. However the concentration of unbound naproxen continues to increase proportionally to dose. NAPRELAN Tablet exhibit similar dose proportional characteristics.

Elimination Metabo

Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes. **Excretion**

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%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66 to 92%). A small amount (<5%) of the drug is excreted in the feces. The rate of excretion has been found to coincide closely with the rate of clearance from the plasma. In patients with renal failure, metabolite 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 Hepatic Impairmen

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose. Renal Imnairmen

Naproxen 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)].

Premature Closure of Fetal Ductus Arteriosus

os/Neonatal Renal Impairmen

Labor or Deliver

arteriosus), use during third trimester should be avoided.

Anaphylactic Reactions

2

APRELAN 2 x 500 mg tablets (1000 mg) Q24h/5 days SD Range 145 1173 - 1774 74 - 127 13 49 - 74 23 - 48 7

2-10

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)] NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

CLINICAL STUDIES

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.

HOW SUPPLIED/STORAGE AND HANDLING

NAPRELAN (na proxen sodium) 375 mg, 500 mg, and 750 mg are controlled-release tablets supplied as:

NAPRELAN 375: white. capsule-shaped tablet with "N" on one side and "375" on the reverse; in bottles of 100; NDC 52427-272-01. Each tablet contains 412.5 mg naproxen sodium equivalent to 375 mg naproxen

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

PHARMACIST: Dispense in a well-closed container

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 NAPRELAN and periodically during the course of ongoing

therapy

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)].

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 NAPRELAN, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalization and even death. Advise patients to stop taking NAPRELAN 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 NAPRELAN, 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 NAPRELAN and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with NAPRELAN 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 NAPRELAN 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.

orm patients not to use low-down as irin concomitantly with NAPRELAN until they talk to their healthcare provider [see Drug Interactions (7)]

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Use of NSAIDS and Low-Dose Aspirin

Morristown, NJ 07960 USA

<u>Analgesia</u>