PRODUCT MONOGRAPH

Pr NAPRELAN®

Naproxen Sodium

375 and 500 mg Controlled Release Tablets
(equivalent to 375 and 500 mg of naproxen base)

Nonsteroidal Anti-Inflammatory Drug (NSAID)

Manufactured by: Alkermes, Inc.
852 Winter Street
Waltham, Massachusetts, USA

Date of Preparation: 14 March 2016

Distributed by: Sunovion Pharmaceuticals Canada Inc.
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NAPRELAN®

naproxen sodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	controlled release tablet/ 375 mg, 500 mg	Not applicable. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NAPRELAN (naproxen sodium) is indicated for the following:

- management of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Throughout this document, the term NSAIDs refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

Use of NAPRELAN should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

NAPRELAN, as a NSAID, does NOT treat clinical disease or prevent its progression.

NAPRELAN, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (> 65 years of age):
Evidence from clinical studies and postmarket experience suggests that use in the geriatric population is associated with differences in safety (see **WARNINGS AND PRECAUTIONS**).

Pediatrics (< 18 years of age):
NAPRELAN is not recommended for use in patients under 18 years of age since safety and effectiveness have not been established.

CONTRAINDICATIONS

NAPRELAN is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although NAPRELAN has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- severe uncontrolled heart failure
- known hypersensitivity to naproxen or to any of the components/excipients
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance – rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **WARNINGS AND PRECAUTIONS – Hypersensitivity Reactions – *Anaphylactoid Reactions***).
- active gastric / duodenal / peptic ulcer, active GI bleeding.
- cerebrovascular bleeding or other bleeding disorders
- inflammatory bowel disease
- severe liver impairment or active liver disease

- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS – Renal**)
- known hyperkalemia (see **WARNINGS AND PRECAUTIONS – Renal – *Fluid and Electrolyte Balance***)
- children and adolescents less than 18 years of age

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (See WARNINGS AND PRECAUTIONS – Cardiovascular).

NAPRELAN is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing NAPRELAN to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as NAPRELAN, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. (see also WARNINGS AND PRECAUTIONS – Renal – *Fluid and Electrolyte Balance*)

Randomized clinical trials with NAPRELAN have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing NAPRELAN.

Risk of Gastrointestinal (GI) Adverse Events (See WARNINGS AND PRECAUTIONS – Gastrointestinal)

Use of NSAIDs, such as NAPRELAN, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

NAPRELAN is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **DRUG INTERACTIONS – Drug/Drug Interactions –** ***Acetylsalicylic acid (ASA) or other NSAIDs***)

NAPRELAN SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN PRODUCTS SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

Cardiovascular

NAPRELAN is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing NAPRELAN to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as NAPRELAN, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing NAPRELAN should hypertension either develop or worsen with its use.

Use of NSAIDs, such as NAPRELAN, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See **WARNINGS AND PRECAUTIONS – Renal – *Fluid and Electrolyte Balance***).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Endocrine and Metabolism

Corticosteroids: NAPRELAN (naproxen sodium) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. (see **DRUG INTERACTIONS – Drug-Drug Interactions – *Glucocorticoids***)

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as NAPRELAN. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with NAPRELAN, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered. (see **WARNINGS AND PRECAUTIONS – Special Populations – *Geriatrics***)

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using NAPRELAN and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

GI adverse reactions reported with NAPRELAN were based on the results from two double-blind clinical trials of three months duration with an additional nine-month open-label extension. During these clinical trials upper GI ulcers and gross bleeding occurred with an incidence of less than 1% with naproxen (see **ADVERSE REACTIONS**). The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.
Caution should be taken if prescribing NAPRELAN to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

NAPRELAN endoscopic effects (see **CLINICAL TRIALS, Special Studies, *Endoscopic Effects*)**

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with NAPRELAN should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed when NAPRELAN is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of NAPRELAN with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

NAPRELAN and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (see **DRUG INTERACTIONS – Drug-Drug Interactions –** ***Acetylsalicylic Acid or other NSAIDs***)

Concomitant administration of NAPRELAN with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias: Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including NAPRELAN. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including NAPRELAN, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients (less than 1% with naproxen, see **ADVERSE REACTIONS**). These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Hepatic 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.

Hypersensitivity Reactions

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to NAPRELAN. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving naproxen. NAPRELAN should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see **CONTRAINDICATIONS**).

ASA-Intolerance: NAPRELAN should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **CONTRAINDICATIONS**).

Cross-sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions: (See **WARNINGS AND PRECAUTIONS – Skin**)

Immune

(See **WARNINGS AND PRECAUTIONS – Infection –** ***Aseptic Meningitis***)

Infection

NAPRELAN, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis: Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as NAPRELAN. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilledema have been reported

in users of NSAIDs including naproxen, although a cause and effect relationship cannot be established. If such symptoms develop NAPRELAN should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving NAPRELAN for an extended period of time.

The use of NAPRELAN may cause photosensitivity. Exposure to sunlight or sunlamps may cause vision changes. Patients should be advised to contact their physician if they experience ophthalmologic reactions from exposure to the sun.

Peri-Operative Considerations

(See **CONTRAINDICATIONS** – Coronary Artery Bypass Graft Surgery)

Psychiatric

(See **WARNINGS AND PRECAUTIONS – Neurologic**)

Renal

Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those that are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate an NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Assessment of renal function in these patients before and during therapy with naproxen is recommended. Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as NAPRELAN, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

NAPRELAN and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with impaired renal function. In these cases, utilization of lower doses of NAPRELAN should be considered and patients carefully monitored.

During long-term therapy, kidney function should be monitored periodically.

Advanced Renal Disease: (See **CONTRAINDICATIONS**)

Fluid and Electrolyte Balance: Use of NSAIDs, such as NAPRELAN, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing NAPRELAN in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS – Cardiovascular**).

Use of NSAIDs, such as NAPRELAN, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics. Electrolytes should be monitored periodically (see **CONTRAINDICATIONS**).

NAPRELAN tablets contain 37.5 mg or 50 mg of sodium (1.5 mEq or 2.0 mEq respectively). This should be considered in patients whose overall intake of sodium must be severely restricted.

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function/Reproduction

The use of NAPRELAN, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impaired fertility and is not recommended in women attempting to conceive.

Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of NAPRELAN should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

The use of NAPRELAN may cause photosensitivity. Exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching, or discoloration. Patients should be advised to contact their physician if they experience a reaction from exposure to sun.

Special Populations

Pregnant Women: NAPRELAN is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see **TOXICOLOGY).**

Caution should be exercised in prescribing NAPRELAN during the first and second trimesters of pregnancy (see **TOXICOLOGY).**

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Nursing Women: The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided (see **CONTRAINDICATIONS**).

Pediatrics: No pediatric studies have been performed with NAPRELAN, thus safety of NAPRELAN in pediatric populations has not been established (see **CONTRAINDICATIONS**).

Geriatrics (> *65* years of age): Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests

Patients on long-term treatment with NAPRELAN should have their blood pressure monitored regularly and an ophthalmologic examination should be carried out at periodic intervals (See **WARNINGS AND PRECAUTIONS, Cardiovascular** and **Ophthalmologic**).

Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should be checked in patients on long-term treatment with NAPRELAN. Additionally, concurrent therapy of NAPRELAN with warfarin requires close monitoring of the international normalized ratio (INR) (See **WARNINGS AND PRECAUTIONS, Hematologic**).

Serum transaminases and bilirubin should be monitored regularly during NAPRELAN therapy (See **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Serum creatinine, creatine clearance and serum urea should be checked in patients during therapy with NAPRELAN. Electrolytes, including serum potassium should be monitored periodically (See **WARNINGS AND PRECAUTIONS, Renal**).

When stopping or starting NAPRELAN therapy; monitoring of plasma lithium concentrations is advised.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred particularly in the elderly.

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.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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. Of these 542 patients, 232 received NAPRELAN tablets, 167 were initially treated with Naprosyn® and 143 were initially treated with placebo.

The most frequent adverse events form the double blind and open label clinical trials were headache (15%), followed by dyspepsia (14%) and flu syndrome (10%).

Adverse Events (AEs) reported in combined rheumatoid arthritis (RA) and osteoarthritis (OA) clinical studies*

*Combined AEs regardless of causality and including AEs reported on active control and/or placebo

TABLE 1: Adverse Events (AEs): Incidence Between 3% and 9% in RA and OA Clinical Studies

Body System	NAPRELAN	Naprosyn®	Placebo
Body as a Whole			
infection	3-9%	1-3%	1-3%
pain (back)	3-9%	3-9%	3-9%
pain	3-9%	3-9%	3-9%
Cardiovascular			
edema	3-9%	1-3%	1-3%
Dermatologic			
skin rash	3-9%	3-9%	3-9%
Gastrointestinal			
abdominal pain	3-9%	3-9%	3-9%
constipation	3-9%	1-3%	3-9%
diarrhea	3-9%	3-9%	3-9%
nausea	3-9%	3-9%	1-3%
Renal			
urinary tract infection	3-9%	1-3%	3-9%
Respiratory			
pharyngitis	3-9%	3-9%	3-9%
rhinitis	3-9%	3-9%	3-9%
sinusitis	3-9%	3-9%	3-9%

TABLE 2: Adverse Events (AEs): Incidence Between 1% and <3% in RA and OA Clinical Studies*

*Combined AEs regardless of causality and including AEs reported on active control and/or placebo

Body System	NAPRELAN	Naprosyn®	Placebo
Body as a Whole			
asthenia	<1%	1-3%	0.0%
fever	1-3%	<1%	1-3%
injury (accident)	1-3%	1-3%	1-3%
pain chest	1-3%	1-3%	1-3%
Cardiovascular			
hypertension	1-3%	1-3%	1-3%
Central Nervous System			
dizziness	1-3%	1-3%	<1%
insomnia	1-3%	1-3%	1-3%
paresthesia	1-3%	1-3%	<1%
Gastrointestinal			
dysphagia	<1%	1-3%	<1%
flatulence	1-3%	1-3%	1-3%
gastritis	<1%	1-3%	1-3%
vomiting	1-3%	1-3%	<1%
Hematologic			
anemia	1-3%	1-3%	0.0%
ecchymosis	<1%	1-3%	1-3%
Metabolic and Nutritional			
hyperglycemia	<1%	<1%	1-3%
peripheral edema	1-3%	1-3%	1-3%
Musculoskeletal			
arthralgia	1-3%	1-3%	<1%
cramps (leg)	1-3%	1-3%	1-3%
joint disorder	<1%	1-3%	1-3%
myalgia	1-3%	1-3%	<1%
tendon disorder	1-3%	1-3%	0.0%
Renal			
cystitis	<1%	1-3%	<1%
Respiratory			
bronchitis	1-3%	1-3%	1-3%
cough increased	1-3%	1-3%	1-3%

TABLE 3: Adverse Events (AEs); Incidence Less Than 1% RA and OA Clinical Studies*

*Combined AEs regardless of causality and including AEs reported on active control and/or placebo

Body as a Whole	Abdomen enlarged, abscess, allergic reaction, carcinoma, cellulitis, edema general, LE syndrome, malaise, monilia, mucous membrane disorder, neck rigid, pain neck, pain pelvic
Cardiovascular	Abnormal electrocardiogram (ECG), angina pectoris, aortic stenosis, arrhythmia, bundle branch block, coronary artery disease, deep thrombophlebitis, heart failure right, hemorrhage, migraine, myocardial infarction, syncope, tachycardia, vascular anomaly, vasculitis, vasodilation
Central Nervous System	Amnesia, anxiety, confusion, co-ordination abnormal, depression, emotional lability, hematoma subdural, hypertonia, nervousness, neuralgia, neuritis, paralysis, vertigo
Dermatologic	Acne, alopecia, dermatitis contact, dry skin, eczema, herpes simplex, herpes zoster, nail disorder, neoplasm skin, pruritus, subcutaneous nodule, ulcer skin, urticaria
Gastrointestinal	Anorexia, cholecystitis, cholelithiasis, colitis, eructation, esophagitis, gastroenteritis, GI disorder, GI hemorrhage, hepatosplenomegaly, liver function abnormality, melena, periodontal abscess, rectal disorder, rectal hemorrhage, stomatitis aphthous, stomatitis ulcer, tooth disorder, ulcer esophagus, ulcer mouth, ulcer stomach, ulcerative stomatitis
Hematologic	Abnormal red blood cell (RBC), abnormal white blood cell (WBC), bleeding time increased, eosinophilia, leukopenia, thrombocytopenia
Metabolic and Nutritional	Albuminuria, alkalosis, blood urea nitrogen (BUN) increased, creatine increase, dehydration, edema, glucose tolerance decrease, glucosuria, hypercholesteremia, hyperuricemia, hypokalemia, serum glutamic oxaloacetic transaminase (SGOT) increase, serum glutamic pyruvic transaminase (SGPT) increase, weight decrease
Musculoskeletal	Bone disorder, bone pain, bursitis, fibrotendinitis, myasthenia, ptosis, spasm general, spontaneous bone fracture
Renal	Carcinoma breast, dysmenorrhea, dysuria, hematuria, kidney calculus, kidney failure, kidney function abnormality, menorrhagia, metrorrhagia, neoplasm breast, nephrosclerosis, nocturia, pain kidney, prostate disorder, pyelonephritis, pyuria, urinary frequency, urinary incontinence, urinary retention, urine abnormal, uterine spasm, vaginitis
Respiratory	Asthma, dyspnea, epistaxis, laryngitis, lung disorder, lung edema, pneumonia, respiratory disorder, respiratory distress
Special Senses	Amblyopia, conjunctivitis, deaf, ear disorder, keratoconjunctivitis, lacrimation disorder, otitis media, pain eye, scleritis, cataract
General	Angioneurotic edema, hypoglycemia

Adverse Events (AEs) (Incidence between 1% and 9%) that have been reported in clinical trials with naproxen, but were not observed in those patients who received NAPRELAN during the controlled clinical trials described above. In view of the similarity of the two products, these events could potentially occur during the administration of NAPRELAN.

Cardiovascular System: Congestive heart failure

Central Nervous System: Aseptic meningitis, cognitive dysfunction, diplopia, dream abnormalities, inability to concentrate, muscle weakness,

Dermatologic: Angiodermatitis, epidermal necrolysis, epidermolysis bullosa, erythema multiforme, photosensitive dermatitis, photosensitivity reactions resembling porphyria cutaneous tarda, skin necrosis, Stevens-Johnson syndrome, sweating

Gastrointestinal: Cardiospasm, hematemesis, jaundice, necrosis, non-peptic GI ulceration, pancreatitis

Hematologic: Agranulocytosis, aplastic anemia, granulocytopenia, hemolytic anemia

Renal: Glomerular nephritis, hyperkalemia, intersitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis

Respiratory: Eosinophilic pneumonitis

General: Anaphylactoid reactions, menstrual disorders, pyrexia (chills and fevers)

Serious Adverse Events (SAEs) (Incidence <1%) that have been reported in clinical trials with naproxen, but were not observed in patients who received NAPRELAN during the controlled clinical trials described above. In view of the similarity of the two products, these events could potentially occur during the administration of NAPRELAN.

Cardiovascular: Palpitations, dyspnea

Central Nervous System: Lightheadedness, drowsiness

Dermatologic: Ecchymoses, purpura, skin eruptions

Gastrointestinal: Heartburn, stomatitis

Special Senses: Hearing disturbances, tinnitus, visual disturbances

General: Thirst

DRUG INTERACTIONS

Drug-Drug Interactions

Acetaminophen: Prolonged concurrent use of acetaminophen with an NSAID may increase the risk of adverse renal effects. Therefore it is recommended that patients be under close medical supervision while receiving such combined therapy.

Acetylsalicylic acid (ASA) or other NSAIDs: The use of NAPRELAN in addition to any other NSAID, including over the counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effect is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Albumin-Bound Drugs: *In vitro* studies have shown that the naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**).

Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.
Concomitant administration of naproxen and ASA is not recommended because naproxen is displaced from its binding sites during the concomitant administration of ASA, resulting in lower plasma concentrations and peak plasma levels.

Antacids: The rate of absorption of naproxen can be altered (increased or decreased) by concomitant administration of antacids but is not adversely influenced by the presence of food.

Anti-coagulants: (see **WARNINGS AND PRECAUTIONS – Hematologic – *Anti-coagulants***)

Anti-hypertensives: Naproxen and other NSAIDs may diminish the anti-hypertensive effect of propranolol, other beta blockers and Angiotensin Converting Enzyme (ACE) inhibitors as well as other antihypertensive agents.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Anti-platelet Agents (including ASA): There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as NAPRELAN (see **WARNINGS AND PRECAUTIONS – Hematologic – *Anti-platelet Effects***).

Cholestyramine: Concomitant administration of cholestyramine can delay the absorption of naproxen, but does not affect its extent.

Cyclosporin: Inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporin and/or the risk of cyclosporin-induced nephrotoxicity. Patients should be carefully monitored during concurrent use.

Digoxin: Concomitant administration of an NSAID with digoxin can result in an increase in digoxin concentrations which may result in digitalis toxicity. Increased monitoring and dosage adjustments of digitalis glycosides may be necessary during and following concurrent NSAID therapy.

Diuretics: Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.

Glucocorticoids: Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increase the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

Lithium: Concurrent administration of NSAIDs with lithium may increase plasma lithium concentrations. Monitoring of plasma lithium concentrations is therefore advised when starting or stopping a NSAID.

Methotrexate: Caution is advised in the concomitant administration of naproxen and methotrexate since naproxen and other non-steroidal anti-inflammatory agents have been reported to reduce the tubular secretion of methotrexate in an animal model, thereby possibly enhancing its toxicity.

Oral Contraceptives: Salicylate effectiveness may be impaired in women taking oral contraceptives. Women taking oral contraceptives may require higher or more frequent aspirin doses for desired clinical effects. Where maintenance of a specific plasma concentration is crucial, salicylate levels should be monitored when oral contraceptives are begun or discontinued.

Oral Hypoglycemics: Caution is advised in concomitant administration of salicylates and sulfonylureas. Some studies show salicylates reduce basal plasma glucose levels, increase glucose tolerances and augment acute insulin response.

Potassium Supplements: Concurrent use of potassium supplements with an NSAID may increase the risk of gastrointestinal side effects including ulceration and hemorrhage.

Probenecid: Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **Warnings and Precautions – *Gastrointestinal***).

Tacrolimus: Although this interaction has not been studied with NAPRELAN, co-administration of tacrolimus and any NSAID may increase the nephrotoxic effect of tacrolimus. Renal function should be monitored when NAPRELAN and tacrolimus are used in combination.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined. Other laboratory tests in patients on naproxen therapy have shown sporadic abnormalities but no definite trend was seen that would indicate potential toxicity.

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. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.
Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Drug-Lifestyle Interactions

Alcohol: Concurrent use of alcohol with an NSAID may increase the risk of gastrointestinal side effects including ulceration and hemorrhage.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see **WARNINGS AND PRECAUTIONS**).

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.

Recommended Dose and Dosage Adjustment

The lowest effective dose of NAPRELAN should be used in every patient. NAPRELAN like other NSAIDs show considerable variation in response. The recommended starting dose of NAPRELAN in adults is two NAPRELAN 375 mg tablets (750 mg) once daily, or two NAPRELAN 500 mg tablets (1000 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 as a single daily dose.

During long-term administration, the dose of NAPRELAN may be adjusted depending on the clinical response of the patient.

In patients who tolerate lower doses of NAPRELAN well, the dose may be increased to three NAPRELAN 500 mg tablets (1500 mg) once daily for limited periods when a higher level of anti-inflammatory 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 TRIALS**). Symptomatic improvement in arthritis usually begins within one week; however, treatment for two weeks may be required to achieve a therapeutic benefit.

Regardless of indication, the dosage should be individualized to achieve effective dose and minimize adverse events, however the maximum daily dose is three NAPRELAN 500 mg (1500 mg) once daily.

To lessen stomach upset, take this medicine after a meal or with food or milk.

Missed Dose

If a dose of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose. Do not double doses.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk.

OVERDOSAGE

Significant naproxen overdosage may be characterized by drowsiness, dizziness, disorientation, heartburn, indigestion, epigastric pain, abdominal discomfort, nausea, vomiting, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis and apnea. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced seizures, but it is not clear whether or not these were drug-related. No evidence of toxicity or late sequelae have been reported five to 15 months after ingestion for three to seven days of doses up to 3000 mg of naproxen. One patient ingested a single dose of 25 g of naproxen and experience mild nausea and indigestion. It is not known what dose of the drug would be life threatening.

Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive care following a NSAID overdose should be employed. Emesis and/or activated charcoal may be indicated following overdose. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. However, hemodialysis may still be appropriate in the management of renal failure.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NAPRELAN contains naproxen sodium, a member of the arylacetic acid group of NSAIDs.

Naproxen has demonstrated anti-inflammatory, analgesic and antipyretic properties. As with other NSAIDs, its mode of action is not fully understood; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Pharmacodynamics

(See **DETAILED PHARMACOLOGY – Pharmacodynamics**)

Pharmacokinetics

NAPRELAN uses the proprietary IPDAS® (Intestinal Protective Drug Absorption System) technology. It is a rapidly disintegrating tablet system combining an immediate release component and a sustained release component of microparticles that are widely dispersed allowing absorption of the active ingredient throughout the GI tract, maintaining blood levels over 24 hours.

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 is present in the dosage form as an immediate release component. The remaining naproxen sodium is coated as microparticles to provide sustained release properties.

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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 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.

TABLE 4: Pharmacokinetic Parameters at Steady State Day 5 (Mean of 24 Subjects)

Parameter (units)	**naproxen 500 mg tablets Q12h (1000 mg)/5 days**			**NAPRELAN 2 x 500 mg tablets (1000 mg) Q24h/5 days**		
	Mean	SD	Range	Mean	SD	Range
AUC_{0-24} (µgxh/mL)	1446	168	1167 – 1858	1448	145	1173 – 1174
C_{max} (µg/mL)	95	13	71 – 117	94	13	74 – 127
C_{avg} (µg/mL)	60	7	49 – 77	60	6	49 – 74
C_{min} (µg/mL)	36	9	13 – 51	33	7	23 – 48
T_{max} (h)	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 occurs in the first 4-6 hours after administration. This coincides with disintegration of the tablet in the stomach, the transit of the sustained release microparticles through the small intestine and into the proximal large intestine. An *in vivo* imaging study has been performed in healthy volunteers which confirms rapid disintegration of the tablet matrix and dispersion of the microparticles.

The absorption rate from the sustained release particulate component of NAPRELAN is slower than that of conventional naproxen sodium tablets. It is this prolongation of drug absorption processes which 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 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 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 exhibits similar dose proportional characteristics.

Metabolism: Naproxen is extensively metabolized to 6-O-desmethyl naproxen and neither the parent nor the metabolites induce metabolizing enzymes.

Excretion: The elimination half-life of NAPRELAN and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2-3 doses of NAPRELAN. 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 (66-92%). 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.

Special Populations and Conditions

Renal Insufficiency: In patients with renal failure metabolites may accumulate.

STORAGE AND STABILITY

Store at room temperature 15-30°C (59-86°F), in well-closed containers. Dispense in a well-closed container with a child-resistant closure.

Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

NAPRELAN contains 412.5 mg or 550 mg of naproxen sodium, equivalent to 375 mg and 500 mg naproxen and 37.5 mg and 50 mg sodium, respectively. Each NAPRELAN tablet also contains the following inactive ingredients: ammonio methacrylate copolymer Type A, ammonio methacrylate copolymer Type B, citric acid, crospovidone, magnesium stearate, methacrylic acid copolymer Type A, microcrystalline cellulose, povidone, and talc. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

Availability of Dosage Forms

NAPRELAN Controlled-Release Tablets:

NAPRELAN 375: white, capsule-shaped, film-coated tablets, debossed with N on one side, and "375" on the other. Packaged in light-resistant bottles of 75 tablets. Each tablet contains 412.5 mg naproxen sodium equivalent to 375 mg naproxen.

NAPRELAN 500: white, capsule-shaped, film-coated tablets, debossed with N on one side and "500" on the other. Packaged in light-resistant bottles of 60 tablets. Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

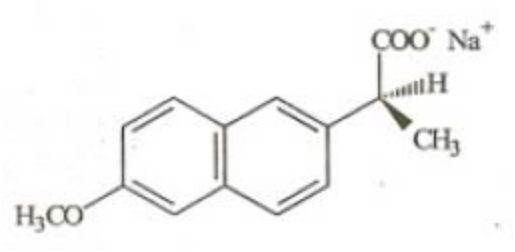
Drug Substance

Proper name: Naproxen sodium

Chemical name: 2-naphthaleneacetic acid, 6-methoxy-α-methyl-sodium salt, (s)-

Molecular formula and molecular mass: $C_{14}H_{13}NaO_3$; 252.24

Structural formula:



Physicochemical properties: Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water.

Solubility: 250 mg/mL in water; 200 mg/mL in methanol; 14 mg/mL in ethanol; 0.102 mg/mL in acetone; 0.04 mg/mL chloroform; 0.014 mg/mL in toluene; and 0.001 mg/mL in benzene

pKa: The pKa of naproxen (free acid) is:
4.39 at an ionic strength of 0.01
4.50 at an ionic strength of 0.1

pH: The pH of a 1 in 20 solution of naproxen sodium in water is between 7.5 and 9.0.

Melting Point: Naproxen sodium melts at about 255°C with decomposition

CLINICAL TRIALS

Randomized clinical trials with NAPRELAN have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Rheumatoid Arthritis

Study Demographics and Trial design

The use of NAPRELAN for the management of the signs and symptoms of rheumatoid arthritis (RA) was assessed in a 12 week double blind, randomized placebo and active-controlled, parallel group comparison study in patients with RA. In the double blind phase of this study, efficacy of NAPRELAN 1000 mg once daily was compared with Naprosyn® 500 mg twice daily and placebo. A total of 348 patients were randomized to treatment, 116 in each group (NAPRELAN, Naprosyn® and placebo). 246 patients completed the double blind phase of the RA study (84 NAPRELAN, 89 Naprosyn® and 73 placebo). All patients received at least one dose of study medication and thus were included in the intent-to-treat analysis. Patients were male and female patients 18 to 75 years of age with a diagnosis of rheumatoid arthritis for at least six months prior to screening. Brief study demographics and trial design for the double blind phase is provided below (Table 5). The primary objective of the double blind study phase was to compare the safety and efficacy of NAPRELAN 1000 mg once daily, Naprosyn® 500 mg twice daily, and placebo given for 12 weeks in patients with rheumatoid arthritis (RA). A secondary objective was to establish equivalent efficacy of controlled-release NAPRELAN 1000 mg once daily and Naprosyn® 500 mg twice daily. Efficacy was evaluated at baseline, then at weeks 1, 2, 4, 8, and 12 (visits 3 through 7).

For the double blind phase of the RA study, efficacy was evaluated and compared among the three treatment groups using the following primary efficacy variables.

- Physician's Global Assessment on the Visit Day (PhyGA)
- Patient's Global Assessment of Condition Since Previous Visit (PtGA)
- Number of Painful Joints (NPJ)-Assessed as pain on palpation and/or motion for all 68 diarthrodial joints, except hips
- Number of Swollen Joints (NSJ)-Assessed as synovial fluid and/or soft tissue swelling, but not bony overgrowth

In the double blind phase of the RA study, analysis was made from the intent-to-treat population. The intent-to-treat analysis compared the mean reductions in each efficacy variable from baseline

(visit 2), at 12 weeks (visit 7) and at the last visit before stopping treatment. A summary of the mean changes from baseline for visit 7 (week 12) is provided (Table 6).

The double blind phase of the RA study was followed by a NAPRELAN open label phase. Patients who completed twelve weeks of double blind therapy were eligible for open label therapy with NAPRELAN 1000 mg once per day and were to continue the open label phase for an additional nine months. A total of 240 patients chose to enroll in the open label phase. Brief study demographics and trial design for the open label phase also provided below (Table 5).

TABLE 5: Summary of patient demographics in patients diagnosed with RA

Trial Design	Dosage	Route of administration and duration	Study subjects n=number	Mean age	Gender
(Double Blind Phase)	NAPRELAN 1000 mg once daily compared with that of placebo and Naprosyn® 500mg bid	Oral 12 wks	n=348	55 years	263 females 85 males
(Open Label Phase)	NAPRELAN 1000 mg once daily	Oral 9 months	n=240	55 years	180 females 60 males

TABLE 6: Summary of Primary Efficacy Variables at Visit 7 (Week 12), for the 12-week, Double Blind Phase, in the Intent-to-Treat Population

Variable[1]	Visit 7 (twelve weeks of treatment)					
	Mean Change ± SEM (standard error of the mean) from Baseline			p-Value		
	NAPRELAN (N = 84)	Naprosyn® (N = 89)	Placebo (N = 73)	NAPRELAN vs. Placebo	Naprosyn® vs. Placebo	NAPRELAN vs. Naprosyn®
PhyGA	3.3 ± 0.2	3.1 ± 0.2	3.0 ± 0.2	0.1386	0.9753	0.1265
PtGA	3.3 ± 0.2	3.4 ± 0.2	2.6 ± 0.3	0.0141 *	0.0125 *	0.9926
NPJ	16.1 ± 1.4	14.2 ± 1.4	15.3 ±1.5	0.0846	0.8499	0.1057
NSJ	8.3 ± 0.9	9.4 ± 0.9	8.9 ± 1.0	0.5511	0.9881	0.5417

[1] PhyGA=Physician's Global Assessment: PtGA=Patient's Global Assessment: NPJ=Number of Painful Joints: NSJ=Number of Swollen Joints

*** statistically significant (p ≤ 0.05), using ANCOVA. The between treatment comparisons favor either the relevant active drug or NAPRELAN for comparison between active drugs.**

Rheumatoid Arthritis, Study Results (Double Blind and Open Label RA Studies)

For the double blind treatment phase of the RA study, the NAPRELAN and Naprosyn® groups were more effective than the placebo group for the Patient's Global Assessment (PtGA) at both visit 7 (week 12) and Endpoint (endpoint data from last available visit for patients failing to complete the full 12 week double blind phase). In addition, at visit 7 (week 12), the NAPRELAN group was better than placebo in the Physician's Global Assessment on the Visit Day (PhyGA). The results from the efficacy variable analysis demonstrated NAPRELAN 1000 mg once daily in the treatment of RA as superior to placebo and at least equivalent to Naprosyn® 500 mg twice daily in PtGA.

For the open label treatment phase of the RA study, those patients initially treated with active drug, either NAPRELAN or Naprosyn® maintained the improvement that they achieved during the double blind phase. For the open label phase, efficacy was limited to the Physicians Global Assessment (PhyGA) and the Patient's Global Assessment (PtGA) with the evaluations performed at Months 4 and 12 (visits 8 and 11). Patients initially treated with placebo showed improvement in PhyGA and PtGA after the first month of NAPRELAN treatment.

Osteoarthritis

Study Demographics and Trial design

The use of NAPRELAN for the management of the signs and symptoms of osteoarthritis (OA) was assessed in a 12 week double blind, placebo and active-controlled study in patients with OA. In the double blind phase of this study, efficacy of NAPRELAN 1000 mg once daily was compared with Naprosyn® 500 mg twice daily and placebo. A total of 347 patients were randomized to treatment, (116 in the NAPRELAN group, 115 in the Naprosyn® group and 116 in the placebo group. 245 patients completed the double blind phase of the OA study. Patients were male and female patients 18 to 80 years of age and a diagnosis of osteoarthritis of the knee for at least six months prior to screening. Brief study demographics and trial design for the double blind phase is provided below (Table 7). The primary objective of the double blind study phase was to compare the safety and efficacy of NAPRELAN 1000 mg once daily, Naprosyn® 500 mg twice daily, and placebo given for 12 weeks in patients with osteoarthritis (OA) of the knee. A secondary objective was to establish equivalent efficacy of controlled-release NAPRELAN 1000 mg once daily and Naprosyn® 500 mg twice daily.

For the double blind phase of the OA study, efficacy was evaluated at baseline, then at weeks 1, 2, 4, 8 and 12 (visits 3 through 7) and compared among the three treatment groups using the following primary efficacy variables.

- Physician's Global Assessment on the Visit Day (PhyGA)
- Patient's Global Assessment of Condition Since Previous Visit (PtGA)
- Severity of Pain Aggravated by Movement (PAM)-Assessed as knee pain on movement measured weight-bearing pain and pain on active/passive movement.
- Severity of Pain on Palpation (POP)-Assessed as severity of knee pain when the investigator palpated the joint.

In the double blind phase of the OA study, analysis was made from the intent-to-treat population. The intent-to-treat analysis compared the mean reductions in each efficacy variable from baseline (visit 2), at 12 weeks (visit 7) and at the last visit before stopping treatment. An assessment of efficacy of all treatment groups was performed after all patients had either completed visit 7 (twelve weeks of treatment) or discontinued the study prior to visit 7 (the last available visit, Endpoint). A summary of the mean changes from baseline for visit 7 (week 12) is provided (Table 8).

The double blind phase of the OA study was followed by a NAPRELAN open label phase. Patients who completed twelve weeks of double blind therapy were eligible for open label therapy with NAPRELAN 1000 mg once per day and were to continue the open label phase for an additional nine months. A total of 228 patients chose to enroll in the open label phase. Brief study demographics and trial design for the open label phase also provided below (Table 7).

TABLE 7: Summary of patient demographics in patients diagnosed with osteoarthritis of the knee

Trial Design	Dosage	Route of administration and duration	Study subjects n=number	Mean age	Gender
(Double Blind Phase)	NAPRELAN 1000 mg od compared with that of placebo and Naprosyn® 500 mg bid	Oral 12 wks	n=347	63.8 years	238 females 109 males
(Open Label Phase)	NAPRELAN 1000 mg once daily	Oral 9 months	n=228	63.7 years	159 females 69 males

TABLE 8: Summary of Primary Efficacy at Visit 7 (Week 12), for the 12-week, Double Blind Phase, in the Intent-to-Treat Population

Variable[1]	Visit 7 (twelve weeks of treatment)					
	Mean Change ± SEM (standard error of the mean) from Baseline			p-Value		
	NAPRELAN (N = 84)	Naprosyn® (N = 84)	Placebo (N = 77)	NAPRELAN vs. Placebo	Naprosyn® vs. Placebo	NAPRELAN vs. Naprosyn®
PhyGA	3.6 ± 0.2	3.6 ± 0.3	2.9 ± 0.3	0.0116 *	0.0310 *	0.6863
PtGA	3.8 ± 0.3	3.9 ± 0.3	2.1 ± 0.3	0.0000 *	0.0000 *	0.8495
PAM	3.6 ± 0.3	3.7 ± 0.3	2.6 ±0.3	0.0154 *	0.0123 *	0.9512
POP	3.2 ± 0.3	3.2 ± 0.3	2.8 ± 0.3	0.1667	0.1475	0.9554

[1] PhyGA=Physician's Global Assessment; PtGA=Patient's Global Assessment; PAM=Pain Aggravated by Movement; POP=Pain on Palpation.

* statistically significant difference ($p \leq 0.05$) using ANOVA.

Osteoarthritis, Study Results (Double Blind and Open Label OA Studies)

For the double blind treatment phase of the OA of the knee study, at the end of 12 weeks of treatment, three of the four primary efficacy variables favored NAPRELAN over placebo. Mean scores in the active-control (naproxen 500 mg bid) treated group were also significantly greater than those in the placebo treated group. NAPRELAN and the active control were equally effective. Thus, NAPRELAN 1000mg once daily and naproxen 500mg tablets twice daily were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study. In the double blind treatment phase, NAPRELAN and Naprosyn® demonstrated comparable efficacy with no significant differences in the mean efficacy scores. After 12-weeks, three of the four primary efficacy variables (PhyGA, PtGA and PAM) favored NAPRELAN and Naprosyn® when compared with placebo.

For the open label treatment phase of the OA of the knee study, evaluation of efficacy was limited to the Physicians Global Assessment (PhyGA) and the Patient's Global Assessment (PtGA) with the evaluations performed at Months 4 and 12 (visits 8 and 11). Patients who initially received either NAPRELAN or Naprosyn® maintained their improvement achieved in the double blind phase. By

contrast, patients who initially received placebo showed improvement in PhyGA and PtGA after the first month of NAPRELAN treatment.

Special Studies

Endoscopic Effects:

Study 1: A double blind, randomized, parallel group study, male subjects received either two NAPRELAN 500 mg tablets (1000 mg) once daily or naproxen 500 mg tablets twice daily (1000 mg) for 7 days. 19 subjects completed the study; 10 evaluable subjects took NAPRELAN and 9 evaluable subjects took naproxen. Following treatment the subjects underwent an endoscopic examination to evaluate the gastroduodenal mucosa for damage. The endoscopic examination was assessed visually and scored using the Euler and Lanza visual analog scales. Mucosal biopsies were taken at endoscopy and mucosal damage was evaluated histologically. Following 7 days of treatment with either NAPRELAN 1000 mg once daily or naproxen 500 mg twice daily, results indicate both products caused significant ($p<0.05$) mucosal change from baseline.

Study 2: A double blind, randomized crossover comparison of NAPRELAN (1000 mg once daily), naproxen (500 mg twice daily) and aspirin (650 mg four times daily). Each of the three administration periods lasted for 7 days, with a washout period of 21 days between administration. Twenty-three (23) subjects (12 males, 11 females) completed the study. The study drugs were administered in random order. Prior to receiving and following dosing of the study drugs, each subject underwent gastroduodenal endoscopy to evaluate the mucosa. The primary objective was to compare levels of mucosal damage to the stomach and duodenum for each of the drug regimens. The primary end points were the total number of erosions in the stomach and the total number in the duodenum. In the stomach the mean number of erosions was 18.32 for ASA, 5.00 for naproxen, and 4.57 for NAPRELAN. The difference between ASA and the other two formulations was significant ($p<0.001$) but there was no significant difference between NAPRELAN and naproxen. In the duodenum the mean number of erosions was 5.91 for ASA, 4.57 for naproxen and 1.83 for NAPRELAN. Mucosal damage in the duodenum was significant for NAPRELAN vs. naproxen ($p=0.024$) and for NAPRELAN vs. ASA ($p=0.009$), but there was no significant difference between naproxen vs. ASA. The clinical significance of these findings is unknown.

DETAILED PHARMACOLOGY

Pharmacokinetics

NAPRELAN Tablet Matrix Disintegration and Bead Dispersion Characteristics: An *in vivo* imaging study was performed to validate the tablet matrix disintegration and bead dispersion characteristics of NAPRELAN under both fasted and fed conditions. This study used a gamma scintigraphy camera and a radioisotope distributed in the controlled release beads. The integrity, distribution and transit characteristics of 1) the intact matrix tablet, 2) the disintegrated tablet and 3) the delayed release beads, plotted under both fasting and fed conditions, also matched the pharmacokinetic profile of the product in a group of healthy volunteers. This technique provides an *in vivo* verification of the rapid disintegration of the tablet, and the subsequent distribution and dispersion of the delayed release beads in the upper and lower small intestine.

Based on the pharmacokinetic profile, it is clear that the absorption phase of NAPRELAN, limited to primarily the first four to six hours after administration, coincides with the disintegration of the tablet in the stomach and the transit of the controlled released beads through the small intestine and into the proximal large intestine. The absorption phase is consistent with a control of the peak plasma concentrations following NAPRELAN administration, rather than being associated with a greatly extended absorption phase, which is unnecessary given the long inherent half life of naproxen. The presence of food did not significantly affect the disintegration or dispersion characteristics of the dosage form in the gastrointestinal tract, nor were the pharmacokinetic characteristics of the product significantly affected.

Food Effect: In addition to the imaging study described above, another study was conducted with NAPRELAN under fasted and fed conditions to determine if the consumption of food had any impact on the pharmacokinetic profile of NAPRELAN.

In a randomized crossover fashion, 24 male volunteers received a single dose of NAPRELAN 500 mg in a fasted state and 30 minutes following a heavy breakfast. Plasma sampling for 48 hours post-dose was conducted. Food was found to have little effect on the *in vivo* pharmacokinetics of NAPRELAN. The rate and extent of absorption, as estimated by AUC_{0-4} and C_{max} was unaffected by food [90% Confidence Interval for NAPRELAN (fed)/NAPRELAN (fasted): $\log_{10}$ AUC_{0-4} = 95.50% - 100.00%; $\log_{10}$ C_{max} = 85.11% - 97.73%]. Administration of NAPRELAN with food resulted in a slight delay in T_{max} [fed T_{max}: 7.42±4.94 hours; fasted T_{max}: 4.13±1.48 hours ($p<0.01$)].

TOXICOLOGY

Three preclinical toxicology studies were conducted with NAPRELAN, as described below. These studies focused on naproxen's effects on the most sensitive organ system, the gastrointestinal tract.

Acute Toxicity

24 hour GI Toxicity Study of NAPRELAN in Dogs: A 24-hour gastrointestinal toxicity study in dogs was undertaken to assess the local irritancy in nine males and nine females. The doses administered were NAPRELAN 1500 mg (equivalent to 500 mg x 3), Naprosyn® 1500 mg (500 mg x 3) for the active control, and preformulated placebo tablets. In each case, intact 500 mg tablets were placed in ligated sections of the duodenum, ileum and colon. The tissue was necropsied 24 hours later and macroscopic and microscopic effects in the mucosa were observed.

There were no clinical signs of toxicity observed upon gross examination or histopathology that could be attributed to the test or control articles. No clinical chemistry data indicated the presence of any abnormalities related to treatment. The only laboratory changes were small increases in BUN and serum creatinine levels in the dogs dosed with NAPRELAN and Naprosyn® when compared to the vehicle controls.

The gross effects were less in the NAPRELAN and Naprosyn® groups than in the placebo group. This was probably due to a reduction of the inflammatory effects by the surgical procedure. There were no signs of chemical irritation. No histological damage could be attributed to the test drugs or control article.

Long-Term Toxicity

Two long term toxicity gastrointestinal studies were conducted with NAPRELAN, similar to each other in design but involving two different species, micro-swine and monkeys. NAPRELAN tablets were administered daily at two dose levels to correspond with the minimum and maximum clinical dose range. The Naprosyn® dose was chosen to mimic low to average clinical dose levels for this product, and provide a relevant baseline for comparison with NAPRELAN.

Repeated Dose Oral Toxicity Study of NAPRELAN in Micro-swine: This study examined the gastrointestinal effects of NAPRELAN through a repeat dose oral toxicity study in micro-swine. The effects of seven days dosing with NAPRELAN daily at two dose levels (500 mg qd or 1500 qd), Naprosyn® (375 mg bid), and placebo on eight males and eight female swine were assessed.

No clinical signs of toxicity were observed. There were small erosions in the mucosa of 2-Naprosyn®, 1-500 mg NAPRELAN, and 2-1500 mg NAPRELAN and 0-placebo treated swine. In general, the erosions with Naprosyn® were deeper and included submucosal inflammation. No abnormal findings were noted during the ophthalmic examinations. No trends in the hematologic or clinical chemistry data suggest the presence of any treatment effects.

Repeated Dose Oral Toxicity Study in NAPRELAN in Rhesus Monkeys: An additional study was conducted in monkeys to confirm the gastrointestinal tolerability of NAPRELAN. This study was very similar in design to that conducted with the micro-swine. Eight male and eight female monkeys were dosed for seven days with either 500 mg or 1500 mg NAPRELAN, 375 mg Naprosyn® bid or placebo.

In contrast to the micro-swine, the monkeys exhibited vomiting with the 1500 mg dose of NAPRELAN. In addition, there was a possible effect on BUN and creatinine in all monkeys who received naproxen. The gastrointestinal mucosa of the fundus and pyloric area exhibited small erosions in the animals that received Naprosyn®. Histopathological examination showed erosions in three monkeys in the 1500 mg group, two in the Naprosyn® group, and none in the other two groups. Only one animal in the 1500 mg NAPRELAN group exhibited reddish streaks in the fundus.

The 500 mg NAPRELAN group demonstrated substantially less gastrointestinal irritation than the other treated animals. The toxicity of NAPRELAN and Naprosyn® was limited to superficial gastric erosions that were associated with local inflammation and occasionally with minute gastric hemorrhage or edema. No abnormal findings were noted during the ophthalmic examinations.

NAPRELAN at 1500 mg dosing was of similar overall toxicity as Naprosyn® dosing at 750 mg. NAPRELAN dosing at 500 mg appeared to be substantially less toxic than either the 1500 mg dose of NAPRELAN or the 750 mg dose of Naprosyn®. Additionally, an observed toxic effect of treatment with 1500 mg NAPRELAN was vomiting.

Reproductive and Developmental Toxicity

Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure) and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug.

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. Naproxen readily crosses the placental barrier.

Canadian Patent 2034096

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PART III: CONSUMER INFORMATION

NAPRELAN®
(naproxen sodium)

Read this information each time you refill your prescription in case new information has been added.

This leaflet is a summary designed specifically for you to read. It will NOT tell you everything about NAPRELAN. See your health care provider and pharmacist regularly and ask them questions about your health and any medications you take.

ABOUT THIS MEDICATION

What the medication is used for:

Your health care provider has prescribed NAPRELAN for you to help in relieving signs and symptoms of rheumatoid arthritis and osteoarthritis.

What it does:

NAPRELAN (naproxen sodium), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals produced by your body which cause pain and swelling.

NAPRELAN, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. NAPRELAN only can relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:

DO NOT TAKE NAPRELAN **if you have any of the following medical conditions:**

- **Heart bypass surgery (planning to have or recently had)**
- **Severe, uncontrolled heart failure**
- **Past or recent history of bleeding in the brain or other bleeding disorders**
- **Current pregnancy (after 28 weeks of pregnancy)**
- **Currently breastfeeding (or planning to breastfeed)**
- **Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs)**
- **Ulcer (active)**
- **Bleeding from the stomach or gut (active)**
- **Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)**
- **Liver disease (active or severe)**
- **Kidney disease (severe or worsening)**
- **High potassium in the blood**

Patients who took a drug in the same class as NAPRELAN after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

NAPRELAN should NOT be used in patients under 18 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:

naproxen sodium

What the nonmedicinal ingredients are:

Each NAPRELAN tablet contains the following inactive ingredients : ammonio methacrylate copolymer Type A, ammonio methacrylate copolymer Type B, citric acid, crospovidone, magnesium stearate, methacrylic acid copolymer Type A, microcrystalline cellulose, povidone, and talc. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

What dosage forms it comes in:

Each tablet contains either 375 mg or 500 mg of naproxen as naproxen sodium in a controlled release tablet.

WARNINGS AND PRECAUTIONS

If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than NAPRELAN:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

Before taking this medication, tell your health care provider if you have any of the following:

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac,

diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives
- Any other medical problems

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other heath care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- fertility may be decreased. The use of NAPRELAN is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping NAPRELAN should be considered.

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs
  - e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
    - e.g. citalopram, fluoxetine, paroxetine, sertraline
- Blood pressure medications
  - ACE (angiotensin converting enzyme) inhibitors
    - e.g. enalapril, lisinopril, perindopril, ramipril
  - ARBs (angiotensin II receptor blockers)
    - e.g. candesartan, irbesartan, losartan, valsartan
- Blood thinners
  - e.g. warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids)
  - e.g. prednisone
- Cyclosporin
- Digoxin
- Diuretics
  - e.g. furosemide, hydrochlorothiazide
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus
- Phenytoin
- Probenecid
- Cholestyramine
- Acetaminophen
- Potassium Supplements
- Alcohol

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking NAPRELAN. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both NAPRELAN and ASA than if you took NAPRELAN alone.

PROPER USE OF THIS MEDICATION

Usual dose:

Medical Condition	Age Group	Starting Dose	Maximum Dose (per day)	Maximum Duration of Treatment (days)
Rheumatoid arthritis and osteoarthritis	Adults (≥18 years of age)	Two 375 mg tablets (750 mg) once daily or two 500 mg tablets (1000 mg) once daily. The usual daily dose of two 500 mg tablets (1000 mg) once daily.	Three 500 mg tablets (1500 mg) once daily.	7 days*

* If you will be using NAPRELAN for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.
If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medicine is not causing unwanted effects.

During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

Be sure to take NAPRELAN regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine.

Take NAPRELAN only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much NAPRELAN may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e., do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.
Do not crush or chew NAPRELAN tablets; swallow tablet whole.

Overdose:

If you take more than the prescribed dose, contact your health care provider immediately.

Missed Dose:

If you miss a dose, take the next regularly scheduled dose and do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

NAPRELAN may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

NAPRELAN may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking NAPRELAN, do NOT drive or operate machinery.

NAPRELAN may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom	STOP taking NAPRELAN and get emergency medical attention IMMEDIATELY	STOP taking NAPRELAN and talk to your physician or pharmacist
Bloody or black tarry stools	✓	
Shortness of breath, wheezing, any trouble breathing or chest tightness	✓	
Skin rash, hives, swelling or itching	✓	
Blurred vision, or any visual disturbance	✓	
Any change in the amount or colour of your urine (red or brown)	✓	
Any pain or difficulty experienced while urinating		✓
Swelling of the feet, lower legs; weight gain		✓
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✓
Yellow discoloration of the skin or eyes, with or without itchy skin		✓
Malaise, fatigue, loss of appetite		✓
Headaches, stiff neck		✓
Mental confusion, depression		✓
Dizziness, lightheadedness		✓
Hearing problems		✓

This is NOT a complete list of side effects. If you develop any other symptoms while taking NAPRELAN, see your health care provider.

HOW TO STORE IT

NAPRELAN should be stored at room temperature (15-30°C/59-86°F) in a closed container.

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.sunovion.ca or by contacting the distributor, Sunovion Pharmaceuticals Canada Inc., at:
1-866-260-6291

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