NAPROXEN - naproxen tablet
REMEDYREPACK INC.

BOXED WARNING

Cardiovascular Risk

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fate. This risk may increase with duration of use. Patient with cardiovascular disease or risk factor for cardiovascular disease may be at great risk (seeWARNINGS).

Naproxen as Naproxen Tablets, USP is contraindicated for the treatment of peri0operative pain in the setting of coronary artery bypass graft (CABG) surgery (seeWARNINGS).

Gastrointestinal Risk

NSAIDs cause increased risk of serious gastrointestinal adverse event including, 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 are at greater risk for serious gastrointestinal events (seeWARNINGS).

DESCRIPTION

Naproxen is a proprionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical name for naproxen is (S)-6-methoxy-a-methyl-2-naphthaleneacetic acid. Naproxen has the following structure:

Naproxen has a molecular weight of 230.26 and a molecular formula of C14H14O3.

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8.

Naproxen Tablets, USP are available as white tablets containing 250 mg of naproxen, white tablets containing 375 mg of naproxen and white tablets containing 500 mg of naproxen for oral administration. The inactive ingredients are Croscarmellose Sodium, Povidone and Magnesium Stearate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

Naproxen is rapidly and completely asorbed from the gastrointestinal tract with an in vivo

bioavailability of 95%. The different dosage forms of naproxen are bioequivalent in terms of extent of absorption (AUC) and peak concentration (Cmax); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 72 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negiligible role in the attainment of steady-state plasma levels.

Absorption

Immediate Release

After administration of Naproxen Tablets, USP, peak plasma levels are attained in 2 to 4 hours.

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough Css 36.5, 49.2, and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma (seePRECAUTIONS: Nursing Mothers).

Metabolism

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

Excretion

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

Special Populations

Geriatric Patients

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is < 1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Race

Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency

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

Renal Insufficiency

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min) (seeWARNINGS: Renal Effects).

CLINICAL STUDIES

General Information

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

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

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

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

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

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

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

effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDS, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

In 51Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen as 1000 mg of Naproxen Tablets, USP has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Geriatric Patients

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

INDICATIONS & USAGE

Carefully consider the potential benefits and risks of Naproxen Tablets, USP and other treatment options

before deciding to use Naproxen Tablets, USP. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (seeWARNINGS).

Naproxen as Naproxen Tablets, USP is indicated:

For the relief of the signs and symptoms of rheumatoid arthritis
For the relief of the signs and symptoms of osteoarthritis
For the relief of the signs and symptoms of ankylosing spondylitis
For the relief of the signs and symptoms of juvenile arthritis
For relief of the signs and symptoms of tendonitis
For relief of the signs and symptoms of bursitis
For relief of the signs and symptoms of acute gout
For the management of pain
For the management of primary dysmenorrhea

CONTRAINDICATIONS

Naproxen Tablets, USP are contraindicated in patients with known hypersensitivity to naproxen. Naproxen Tablets, USP should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (seeWARNINGS: Anaphylactoid ReactionsandPRECAUTIONS: Preexisting Asthma).

Naproxen Tablets, USP are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (seeWARNINGS).

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (seeGastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (seeCONTRAINDICATIONS).

Hypertension

NSAIDs, including Naproxen Tablets, USP, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Naproxen Tablets, USP, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs. Naproxen Tablets, USP should be used with caution in patients with fluid retention, hypertension, or heart failure.

Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including Naproxen Tablets, USP, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.

These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs 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 with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious GI adverse event on NSAID therapy is symptomatic.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. 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 in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver disfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state (see<u>WARNINGS: Advanced Renal Disease).</u>

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of Naproxen Tablets, USP in patients with advanced renal disease. Therefore, treatment with Naproxen Tablets, USP is not recommended in these patients with advanced renal disease. If Naproxen Tablets, USP therapy must be initiated, close monitoring of the patientrenal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Naproxen Tablets, USP. Naproxen Tablets, USP should not be given to patients with the aspirin 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 aspirin or other NSAIDs (see<u>CONTRAINDICATIONSandPRECAUTIONS: Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.</u>

Skin Reactions

NSAIDs, including Naproxen Tablets, USP, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first

appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, Naproxen Tablets, USP should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

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

Naproxen Tablets, USP cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

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

The pharmacological activity of Naproxen Tablets, USP in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

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

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including Naproxen Tablets, USP. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continuing therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with Naproxen Tablets, USP.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Naproxen Tablets, USP should be discontinued.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Hematological Effects

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

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving Naproxen Tablets, USP who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross

reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Naproxen Tablets, USP should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAIDMedication Guide that accompanies each prescription dispensed.

1. Naproxen Tablets, USP, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (seeWARNINGS: Cardiovascular Effects).

2. Naproxen Tablets, USP, 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. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (seeWARNINGS: Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation).

3. Naproxen Tablets, USP, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, andsymptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (seeWARNINGS).

7. In late pregnancy, as with other NSAIDs, Naproxen Tablets, USP should be avoided because it may cause premature closure of the ductus arteriosus.

8. Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, Naproxen Tablets, USP should be discontinued.

Drug Interactions

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Antacids and Sucralfate

Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.

Aspirin

When naproxen as Naproxen Tablets, USP is administered with aspirin, its protein binding is reduced, although the clearance of free Naproxen Tablets, USP is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of naproxen and aspirin is not generally recommended because of the potential of increased adverse effects.

Cholestyramine

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that Naproxen Tablets, USP can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS: Renal Effects), as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

Other Information Concerning Drug Interactions

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonyulreas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphylurea should be observed for adjustment of dose is required.

Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

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

Drug/Laboratory Test Interactions

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

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).

Carcinogenesis

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

Pregnancy
Teratogenic Effects
Pregnancy Category C
Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Naproxen Tablets, USP should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects
There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.
Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage. The effects of Naproxen Tablets, USP on labor and delivery in pregnant women are unknown.
Nursing Mothers
The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.
Pediatric Use
Safety and effectiveness in pediatric patients below the age of 2 years have not been established.
Geriatric Use
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.
Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population (see WARNINGS).
Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs (see WARNINGS: Renal Effects).

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

gastrointestinal tract.
A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (seeCLINICAL PHARMACOLOGY).
In controlled clinical trials with about 80 pediatric patients and in well monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.
In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:
Gastrointestinal (GI) Experiences, including:heartburn1, abdominal pain1, nausea1, constipation1, diarrhea, dyspepsia, and stomatitis
Central Nervous System:headache1, dizziness1, drowsiness1, lightheadedness, vertigo
Dermatologic:pruritus (itching)1, skin eruptions1, ecchymoses1, sweating, purpura
Special Senses: tinnitus1, visual disturbances, hearing disturbances
Cardiovascular: edema1, palpitations.
General:dyspnea1, thirst
In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients.
Gastrointestinal (GI) Experiences, including:flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting
General:abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes
The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through postmarketing reports are italicized.
Body as a Whole:anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)
Cardiovascular:congestive heart failure, vasculitis, hypertension, pulmonary edema
Gastrointestinal:gastrointestinal bleeding and/or perforation, hematemesis, pancreatitis, vomiting, colitis, nonpeptic gastrointestinal ulceration, ulcerative stomatitis, peptic ulceration
Hepatobiliary:jaundice, abnormal liver function tests, hepatitis (some cases have been fatal)
Hemic and Lymphatic:eosinophilia, leucopenia, melena, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia
Metabolic and Nutritional:hyperglycemia, hypoglycemia
Nervous System: inability to concentrate, depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions
Respiratory:eosinophilic pneumonitis, asthma
Dermatologic:alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythemia multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematosus, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.
Special Senses:hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema
Urogenital:glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine
Reproduction (female):infertility
In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.
Body as a Whole:fever infection, sepsis, anaphylactic reactions, appetite changes, death

Cardiovascular:hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction
Gastrointestinal:dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation
Hepatobiliary:hepatitis, liver failure
Hemic and Lymphatic:rectal bleeding, lymphadenopathy, pancytopenia
Metabolic and Nutritional:weight changes
Nervous System:anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations
Respiratory:asthma, respiratory depression, pneumonia
Dermatologic:exfoliative dermatitis
Special Senses:blurred vision, conjunctivitis
Urogenital:cystitis, dysuria, oliguria/polyuria, proteinuria
1 Incidence of reported reaction between 3% and 9%. Those reactions occuring in less than 3% of the patients are unmarked.

OVERDOSAGE

Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.
Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

DOSAGE & ADMINISTRATION

Carefully consider the potential benefits and risks of Naproxen Tablets, USP and other treatment options before deciding to use Naproxen Tablets, USP. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (seeWARNINGS).
After observing the response to initial therapy with Naproxen Tablets, USP, the dose and frequency should be adjusted to suit an individual patient's needs.
Different dose strengths and formulations (i.e., tablets, suspension) of the drug are not necessarily bioequivalent. This difference should be taken into consideration when changing formulation.
Although naproxen tablets, naproxen suspension, naproxen delayed-release tablets, and naproxen sodium tablets all circulate in the plasma as naproxen, they have pharmacokinetic differences that may affect onset of action. Onset of pain relief can begin within 1 hour in patients taking naproxen.
The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (seeWARNINGSandPRECAUTIONS).

Geriatric Patients

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.

Patients With Moderate to Severe Renal Impairment

Naproxen-containing products are not recommended for use in patients with moderate to severe and

severe renal impairment (creatinine clearance <30 mL/min) (seeWARNINGS: Renal Effects).

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

Naproxen Tablets, USP250 mgtwice dailyor 375 mgtwice dailyor 500 mgtwice daily

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for limited periods of up to 6 months when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk. The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response (seeCLINICAL PHARMACOLOGY).

Acute Gout

The recommended starting dose is 750 mg of Naproxen Tablets, USP followed by 250 mg every 8 hours until the attack has subsided.

HOW SUPPLIED

Naproxen Tablets, USP:

250 mg:white, round, biconvex, debossed with "IP 188" on obverse and "250" on the reverse. Packaged in bottles of 100, 500 and 1000.

375 mg:white, capsule-shaped, biconvex, debossed with "IP 189" on obverse and "375" on the reverse. Packaged in bottles of 100, 500 and 1000.

500 mg:white, capsule-shaped, biconvex, debossed with "IP 190" on obverse and "500" on the reverse. Packaged in bottles of 100, 500 and 1000.

STORAGE AND HANDLING

Store at 15-30 C (59-86 F) in well-closed containers; dispense in light-resistant containers.

MEDGUIDE

Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.This chance increases:

with longer use of NSAID medicinesin people who have heart disease**NSAID medicines should never be used right before or after a heart surgery called a artery bypass graft (CABG).**

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

can happen without warning symptomsmay cause death**The chance of a person getting an ulcer or bleeding increases with:**

taking medicines called anddrinking alcohollonger useolder agesmokinghaving poor health**NSAID medicines should only be used:**

exactly as prescribedfor the shortest time neededat the lowest dose possible for your treatment**What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

NSAID medicines 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 a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine

for pain right before or after heart bypass surgery

Tell your healthcare provider:

about all of your medical conditions.

about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects.**Keep a list of your medicines to show to your healthcare provider and pharmacist.**

if you are pregnant.**NSAID medicines should not be used by pregnant women late in their pregnancy.**

if you are breastfeeding.**Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:Other side effects include:heart attack

stroke

high blood pressure

heart failure from body swelling (fluid retention)

kidney problems including kidney failure

bleeding and ulcers in the stomach and intestine

low red blood cells (anemia)

life-threatening skin reactions

life-threatening allergic reactions

liver problems including liver failure

asthma attacks in people who have asthmastomach pain

constipation

diarrhea

gas

heartburn

nausea

vomiting

dizziness**Get emergency help right away if you have any of the following symptoms:**

shortness of breath or trouble breathingslurred speechchest painswelling of the face or throatweakness in one part or side of your body**Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:**

nauseavomit bloodmore tired or weaker than usualthere is blood in your bowel movement or it is black and sticky like taritchingunusual weight gainyour skin or eyes look yellowskin rash or blisters with feverstomach painswelling of the arms and legs, hands and feetflu-like symptomsThese are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.

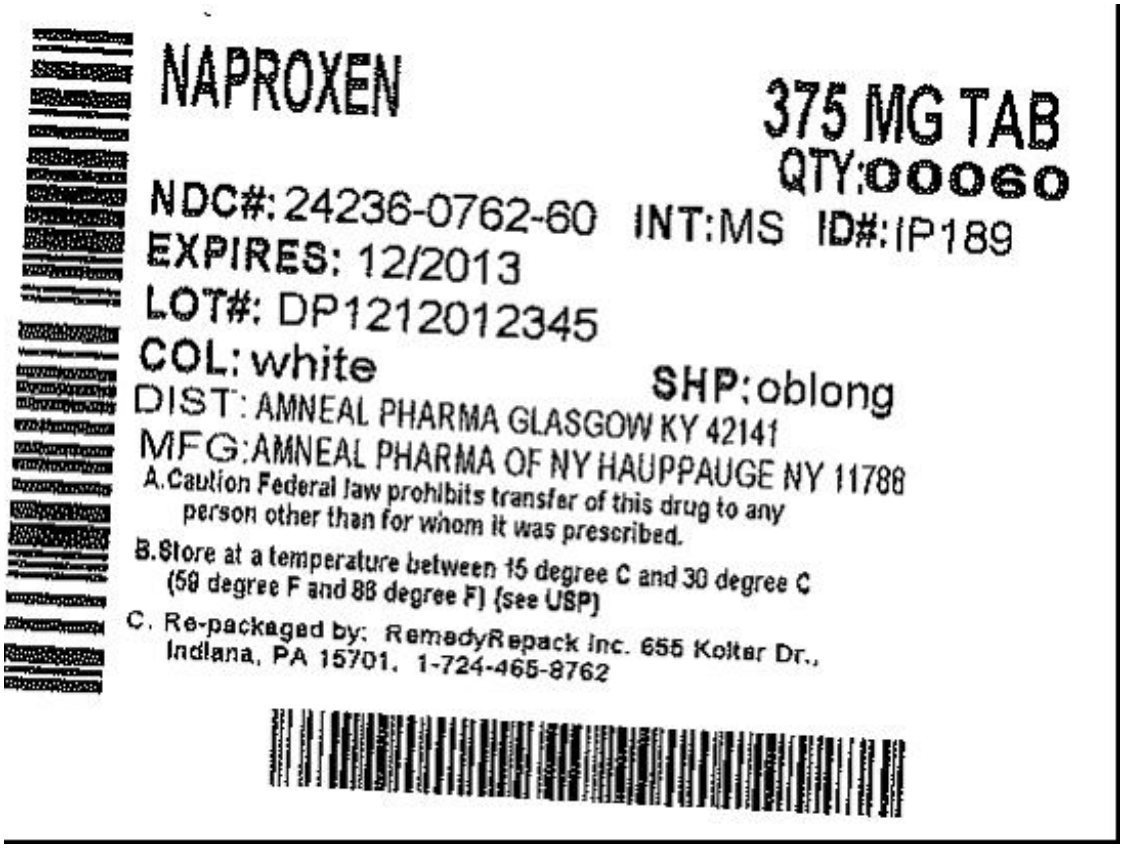
Some of these NSAID medicines are sold in lower doses without a prescription (overthe-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic NameTradename CelecoxibCelebrexDiclofenacCataflam, Voltaren, Arthrotec (combined with misoprostol)DiflunisalDolobidEtodolacLodine, Lodine XLFenoprofenNalfon, Nalfon

200FlurbiprofenAnsaidIbuprofenMotrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)IndomethacinIndocin, Indocin SR, Indo-Lemmon, IndomethaganKetoprofenOruvailKetorolacToradolMefenamic AcidPonstelMeloxicamMobicNabumetoneRelafenNaproxenNaprosyn, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)OxaprozinDayproPiroxicamFeldeneSulindacClinorilTolmetinTolectin, Tolectin DS, Tolectin 600* Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION
DRUG: NAPROXEN
GENERIC: NAPROXEN
DOSAGE: TABLET
ADMINSTRATION: ORAL
NDC: 24236-762-60
STRENGTH:375 mg
COLOR: white
SHAPE: CAPSULE
SCORE: No score
SIZE: 14 mm
IMPRINT: 60
QTY: 60



NAPROXEN

naproxen tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:24236-762(NDC:53746-189)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NAPROXEN (UNII: 57Y76R9ATQ) (NAPROXEN - UNII:57Y76R9ATQ)	NAPROXEN	375 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE (UNII: FZ989GH94E)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	white	**Score**	no score
Shape	CAPSULE (TABLET)	**Size**	14mm
Flavor		**Imprint Code**	IP189;375
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:24236-762-60	60 in 1 VIAL		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075927	01/10/2013	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 1/2013 REMEDYREPACK INC.