NAPROXEN SODIUM - naproxen sodium tablet
AvKARE, Inc.

NAPROXEN SODIUM TABLETS, USP
OT910
Rx only

Cardiovascular Risk

• NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use, Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**),

• Naproxen as Naproxen Sodium Tablets, USP is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**),

Gastrointestinal Risk

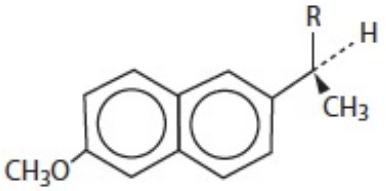
• NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

These events can occur at any time during use and without warning symptoms, Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

DESCRIPTION

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

The chemical name for naproxen sodium is (S)-6-methoxy-a-methyl-2-naphthalene acetic acid, sodium salt. Naproxen sodium has the following structure:



naproxen sodium (R=-COONa) $C_{14}H_{13}NaO_3$ mol wt 252.23

Naproxen sodium molecular weight of 252.23 and a molecular formula of $C_{14}H_{13}NaO_3$.

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

Naproxen Sodium Tablets, USP are available as blue tablets containing 275 mg of naproxen sodium and as blue tablets containing 550 mg of naproxen sodium. The inactive ingredients are croscarmellose sodium, macrogol, magnesium stearate, polyvinly alcohol, povidone, talc, titanium dioxide and FD&C Blue # 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. 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 sodium is rapidly and completely absorbed 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 (C_{max}); 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 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption

Immediate release

After oral administration of naproxen sodium, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in naproxen sodium.

Distribution

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

Metabolism

Naproxen is extensively metabolized in the liver to 6-*O*-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-*O*-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-*O*-desmethyl naproxen (< 1%), or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen 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 (see **WARNINGS: Renal Effects**).

Special Populations

Pediatric Patients

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see **DOSAGE AND ADMINISTRATION**) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in

pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients.

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 have not been determined in subjects with hepatic insufficiency.

Renal Insufficiency

Naproxen pharmacokinetics have 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) (see **WARNINGS: 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 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1100 mg of Naproxen Sodium 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 AND USAGE

Carefully consider the potential benefits and risks of Naproxen Sodium Tablets, USP and other treatment options before deciding to use Naproxen Sodium Tablets, USP. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

Naproxen suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the patient’s weight.

Naproxen as naproxen sodium tablets are 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 dysmenorrheal

CONTRAINDICATIONS

Naproxen Sodium Tablets, USP are contraindicated in patients with known hypersensitivity to naproxen and naproxen sodium.

Naproxen Sodium 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 (see **WARNINGS: Anaphylactoid Reactions** and **PRECAUTIONS: Preexisting Asthma**).

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

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 (see **Gastrointestinal 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 (see **CONTRAINDICATIONS**).

Hypertension

NSAIDs, including Naproxen Sodium Tablets, USP, can lead to onset of new hypertension or worsening of pre-existing 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 Sodium 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 Sodium Tablets, USP should be used with caution in patients with fluid retention, hypertension, or heart failure. Since each Naproxen Sodium Tablet, USP contains 25 mg or 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), this should be considered in patients whose overall intake of sodium must be severely restricted.

Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including Naproxen Sodium 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 to 6 months, and in about 2 to 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 non-steroidal 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 dysfunction, salt depletion, those taking diuretics and ACE- inhibitors, and the elderly. Discontinuation of non-steroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state (see **WARNINGS: Advanced Renal Disease**).

Advanced Renal Disease

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

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Naproxen Sodium Tablets, USP. Naproxen Sodium 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 **CONTRAINDICATIONS** and **PRECAUTIONS: Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including Naproxen Sodium 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 Sodium Tablets, USP should be avoided because they may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

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

Naproxen Sodium 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 long-term therapy should have hemoglobin values determined periodically.

The pharmacological activity of Naproxen Sodium 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 Sodium 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 continued 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 a more severe hepatic reaction while on therapy with Naproxen Sodium Tablets, USP.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Naproxen Sodium 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 Sodium 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 Sodium 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 Sodium 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 non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Naproxen Sodium 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 NSAID Medication Guide that accompanies each prescription dispensed.

1. Naproxen Sodium 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 signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS: Cardiovascular Effects**).
2. Naproxen Sodium 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 (see **WARNINGS:Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**).
3. Naproxen Sodium Tablets, USP, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalization 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, and "flu-like" symptoms). 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 (see **WARNINGS**).
7. In late pregnancy, as with other NSAIDs, Naproxen Sodium Tablets, USP should be avoided because they 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 Sodium 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 Sodium Tablets, USP is administered with aspirin, its protein binding is reduced, although the clearance of free Naproxen Sodium Tablets, USP is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of naproxen and naproxen sodium 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 Sodium 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 sodium and other non-steroidal 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 non-steroidal 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, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Naproxen and other non-steroidal 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/m^2). 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/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. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Naproxen Sodium 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 non-steroidal 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 Sodium 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. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see **DOSAGE AND ADMINISTRATION**). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen suspension, see **DOSAGE AND ADMINISTRATION**), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

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 non-steroidal 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 a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of non-steroidal 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 (see **CLINICAL 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: heartburn[1], abdominal pain[1], nausea[1], constipation[1], diarrhea, dyspepsia, stomatitis

Central Nervous System: headache[1], dizziness[1], drowsiness[1], lightheadedness, vertigo

Dermatologic: pruritus (itching)[1], skin eruptions[1], ecchymoses[1], sweating, purpura

Special Senses: tinnitus[1], visual disturbances, hearing disturbances

Cardiovascular: edema[1], palpitations

General: dyspnea[1], 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, esophagitis, peptic ulceration*

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

Hemic and Lymphatic: *eosinophilia, leucopenia, 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, erythema multiforme, erythema*

nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, 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

Incidence of reported reaction between 3% and 9%. Those reactions occurring 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. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.

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 AND ADMINISTRATION

Carefully consider the potential benefits and risks of naproxen sodium tablets and other treatment options before deciding to use naproxen sodium tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

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

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 30 minutes in patients taking naproxen sodium and within 1 hour in patients taking naproxen. Because naproxen delayed-release tablets dissolve in the small intestine rather than in the stomach, the absorption of the drug is delayed compared to the other naproxen formulations (see **CLINICAL PHARMACOLOGY**).

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 (see **WARNINGS** and **PRECAUTIONS**).

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) (see **WARNINGS: Renal Effects**).

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

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

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and 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 sodium 1650 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 sodium 1650 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 (see **CLINICAL PHARMACOLOGY**).

Juvenile Arthritis

For the relief of juvenile arthritis, the recommended dose is approximately 10 mg/kg given orally in 2

divided doses (i.e., 5 mg/kg given twice a day). Naproxen sodium tablets are not well suited to this dosage so use of naproxen oral suspension is recommended for this indication.

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

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

Acute Gout

The recommended starting dose is 825 mg of Naproxen Sodium Tablets, USP followed by 275 mg every 8 hours until the attack has subsided.

HOW SUPPLIED

Naproxen Sodium Tablets, USP 275 mg are blue, oval, biconvex, film coated tablets debossed “IP193” on obverse and plain on reverse. They are available as follows:

Bottles of 100: NDC 42291-531-01

Naproxen Sodium Tablets, USP 550 mg are blue, oval, biconvex, film coated tablets debossed “IP” bisect “194" on obverse and plain on reverse. They are available as follows:

Bottles of 100: NDC 42291-532-01
Bottles of 500: NDC 42291-532-50

Store at 15° to 30°C (59°F to 86°F) in well-closed containers

Manufactured for:

AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 10/08
AV Rev. 12/12 (P)

Principal Display Panel

275mg Label

AvKARE

NDC 42291-531-01

Naproxen Sodium
Tablets, USP

275 mg

100 Tablets Rx Only

Each tablet contains:
Naproxen Sodium, USP.....275mg

Pharmacist: Dispense with a Medication Guide.

Usual Dosage: For dosage recommendations and other important prescribing information, read accompanying insert.

Store at 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature] in well-closed containers.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 07/10 AV Rev. 12/12 (P)

N 3 42291 53101 7

550 mg Label

Label Text

AvKARE

NDC 42291-532-50

Naproxen Sodium
Tablets, USP

550 mg

500 Tablets Rx Only

Each tablet contains:
Naproxen Sodium, USP.....550mg

Pharmacist: Dispense with a Medication Guide.

Usual Dosage: For dosage recommendations and other important prescribing information read accompanying insert.

Store at 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature] in well-closed containers.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 07/10 AV Rev. 12/12 (P)

N3 42291 53250 2

NAPROXEN SODIUM

naproxen sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:42291-531(NDC:53746-193)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NAPROXEN SODIUM (NAPROXEN)	NAPROXEN SODIUM	275 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
Polyethylene Glycols	
POLYVINYL ALCOHOL	
MAGNESIUM STEARATE	
POVIDONE	
TALC	
TITANIUM DIOXIDE	
FD&C BLUE NO. 2	

Product Characteristics

Color	BLUE	**Score**	no score
Shape	OVAL	**Size**	13mm
Flavor		**Imprint Code**	IP193
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-531-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078432	04/26/2007	

NAPROXEN SODIUM

naproxen sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:42291-532(NDC:53746-194)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NAPROXEN SODIUM (NAPROXEN)	NAPROXEN SODIUM	550 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
MAGNESIUM STEARATE	
POVIDONE	
TALC	
TITANIUM DIOXIDE	
Polyethylene Glycols	
POLYVINYL ALCOHOL	
FD&C BLUE NO. 2	

Product Characteristics

Color	BLUE	**Score**	no score
Shape	OVAL	**Size**	18mm
Flavor		**Imprint Code**	IP;194
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-532-50	500 in 1 BOTTLE		

2	NDC:42291-532-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078432	04/26/2007	

Labeler - AvKARE, Inc. (796560394)

Revised: 10/2009 AvKARE, Inc.