PRODUCT MONOGRAPH

RIVA-NAPROXEN

(Naproxen)

250 mg, 375 mg and 500 mg Tablets, USP

Anti–Inflammatory Agent with Analgesic and Antipyretic Properties

Laboratoire Riva Inc.
Blainville, Canada

Date of Preparation:

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Control Number: 062636

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THERAPEUTIC CLASSIFICATION

Anti–Inflammatory Agent with Analgesic and Antipyretic Properties

ACTIONS AND CLINICAL PHARMACOLOGY

Naproxen has demonstrated anti–inflammatory, analgesic and antipyretic properties in classical animal test systems. In patients with rheumatoid arthritis the anti–inflammatory action has been shown by a reduction in joint swelling, pain, and duration of morning stiffness, and by enhanced grip strength and increased mobility. It exhibits an anti–inflammatory effect even in adrenalectomized animals and, therefore, its action is not mediated through the pituitary–adrenal axis. It is not a corticosteroid.

During clinical trials, naproxen has been found to be less likely to cause gastrointestinal bleeding in doses usually used than is acetylsalicylic acid.

Clinical trials in man have shown the clinical activity of 500 mg of naproxen daily to be similar to that of 3.6 grams of acetylsalicylic acid daily.

Pharmacokinetics:

Naproxen is rapidly and completely absorbed from the gastrointestinal tract. After oral administration of naproxen, peak plasma levels of naproxen anion are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4-5 doses. Plasma naproxen levels and areas under plasma concentration vs. time curves increased linearly with dose increments up to 500 mg twice a day, but larger doses resulted in a plateau effect. The mean biological half-life of the anion in humans is approximately 13 hours, and at therapeutic levels it is greater than 99% albumin bound. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-0-desmethyl naproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes.

A comparative, two–way crossover bioavailability study was performed on two 250 mg naproxen tablet products, RIVA-NAPROXEN 250 mg tablets, and NAPROSYN® 250 mg tablets. The pharmacokinetic plasma data (mean ± standard deviation) calculated for the RIVA-NAPROXEN and NAPROSYN® tablet formulations is tabulated below:

Pharmacokinetic Indices for Naproxen

	RIVA-NAPROXEN 250 mg	NAPROSYN®**250 mg
Area Under the Curve:(µg•hours/mL); 0-24 hours	499.0 ± 76.7	497.0 ± 60.5
Peak Concentration:Cmax (µg/mL)	46.9 ± 7.6	49.0 ± 7.0
Time of Peak Level:Tmax (hours)	2.5 ± 1.1	1.8 ± 1.0
Elimination Half-Life: $T_{½}$ (hours)	9.87 ± 1.30	9.63 ± 0.90
Elimination Rate Constant:Kel (hour-1)	0.07 ± 0.01	0.07 ± 0.01

INDICATIONS AND CLINICAL USE

RIVA-NAPROXEN (naproxen) is indicated for the treatment of osteoarthiritis, rheumatoid arthritis and ankylosing spondylitis.

Modified release formulations of naproxen (i.e. sustained release) are not recommended for initial treatment of acute pain because the absorption of naproxen is delayed.

CONTRAINDICATIONS

RIVA-NAPROXEN (naproxen) is contraindicated in patients with active peptic ulcers, a history of recurrent ulceration, or active inflammatory diseases of the gastro-intestinal tract. RIVA-NAPROXEN is also contraindicated in patients who have known or suspected hypersensitivity to it or to naproxen sodium or to other non-steroidal anti-inflammatory drugs. The potential for cross-reactivity between different NSAIDs must be kept in mind. RIVA-NAPROXEN should not be given to patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, rhinitis, urticaria, or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory drugs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

RIVA-NAPROXEN is contraindicated in patients with significant hepatic impairment, active liver disease and in patients with severely impaired or deteriorating renal function (creatinine clearance <30mL/min or 0.5 mL/s). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored. RIVA-NAPROXEN is not recommended for use with other NSAIDs because of the absence of any evidence demontrating synergistic benefits and the potential for additive side effects.

RIVA-NAPROXEN is contraindicated in children under 2 years of age since safety in this age group has not been established.

WARNINGS

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAID's) including RIVA-NAPROXEN (naproxen).

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

RIVA-NAPROXEN should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their hemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, RIVA-NAPROXEN should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anti-coagnlant use have been associated with increased risk.

Use in the elderly

Patients older than 65 years and frail or debilitated patients are more susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's): the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to the effects of ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

Cross-sensitivity

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

Aseptic Meningitis

In occasional cases, with some NSAIDs the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be predisposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Use in pregnancy, labour and lactation

The safety of this drug in pregnancy and lactation has not been established and its use is therefore not recommended. Reproduction studies have been performed in rats, rabbits and mice. In rats, pregnancy was prolonged when naproxen was given before the onset of labor, and when given after the delivery process had begun, labor was protracted. Similar results have been found with other non-steroidal anti-inflammatory agents and the evidence suggests that this may be due to decreased uterine contractility resulting from the inihibition of prostaglandin synthesis. This may also increase the risk for uterine hemorrhage. Moreover, because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. RIVA-NAPROXEN (naproxen) readily crosses the placental barrier. It has also been found in the milk of lactating women at a concentration approximately 1% of that found in the plasma.

PRECAUTIONS

RIVA-NAPROXEN (naproxen) should not be used concomitantly with the related drug naproxen sodium since they both circulate in plasmas the naproxen anion.

Gastro-intestinal system

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of RIVA-NAPROXEN therapy when and if these adverse reactions appear.

Renal Function

Long term administration of nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive 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 may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, extracellular volume depletion, sodium restrictions, heart failure, liver dysfunction, those taking diuretics, and the elderly. Assessment of renal function in these patients before and during therapy with naproxen is recommended. Discontinuation of non-steroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

RIVA-NAPROXEN and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with impaired renal function or a history of kidney disease, because naproxen is an inhibitor of prostaglandin biosynthesis. In these cases, utilization of lower doses of RIVA-NAPROXEN should be considered and patients carefully monitored.

Naproxen should not be used chronically in patients having baseline creatinine clearance less than 20 mL/minute. During long term therapy, kidney function should be monitored periodically.

Genitourinary tract

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with RIVA-NAPROXEN must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic function

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients (less than 1% with naproxen). These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction

.vhile on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with non-steroidal anti-inflammatory drugs.

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

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

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown, but caution is advised when high doses are required. It is prudent to use the lowest effective dose.

Steroids

If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

.uid and Electrolyte Balance

Peripheral edema has been observed in some patients receiving naproxen. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Although sodium retention has not been reported in metabolic studies, the drug should be used with caution in patients with fluid retention, hypertension or heart failure.

With non steroidal anti-inflammatory drug treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with beta-andrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when RIVA-NAPROXEN is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of non-steroidal anti-inflammatory drugs are rare (all less than 1% with naproxen), but could be with severe consequences.

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

Infection

The anti-inflammatory, antipyretic and analgesic effects of RIVA-NAPROXEN (naproxen) may mask the usual signs of infection.

Ophthalmology

Bluried and/or diminished vision has been reported with the use of naproxen and other nonsteroidal anti-inflammatory drugs. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilledema have been reported in users of NSAIDs including naproxen, although a cause and effect relationship cannot be established. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examinatons should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Central Nervous System

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of RIVA-NAPROXEN. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Hypersensitivity

Anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (e.g., aspirin syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated non-steroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

Dermatology

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Use in the elderly patient

One study indicates that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The implication of this finding for naproxen dosing is unknown, but caution is advised when high doses are required. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Drug Interactions

Acetylsalicylic acid (ASA) or other NSAIDs:

The use of RIVA-NAPROXEN (naproxen) in addition to any other NSAID, including those over the counter ones (such as ASA and ibuprofen) is not recommended due to the possibility of additive side effects.

Anticoagulants:

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.

Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet function, concurrent therapy of RIVA-NAPROXEN with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

Albumin-Bound Drugs:

The naproxen anion may displace from their binding sites other drugs which are also albumin- bound and may lead to drug interactions. For example, in patients receiving bishydroxycomarin or warfarin; the addition of RIVA-NAPROXEN could prolong the prothrombin time. These patients should therefore be under carefull observation. Similarly, patients receiving RIVA-NAPROXEN and a hydantoin, sulfonamide or sulfonylurea should be observed for adjustment of dose if required.

Diuretics:

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class.

Lithium:

Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations have also been reported.

Antihypertensive Drugs:

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta blockers as well as other antihypertensive agents.

Antacids:

The rate of absorption of naproxen is altered by concomitant administration of antacids but is not adversely influenced by the presence of food.

Probenecid:

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

Cholestyramine:

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

Methotrexate:

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

Glucocorticoids:

Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Acetaminophen:

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

Alcohol/Potassium Supplements:

Concurrent use of alcohol or potassium supplements with an NSAID may increase the risk of gastrointestinal side effects including ulceration and hemmorhage.

Cyclosporine:

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

Digoxin:

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

Laboratory Tests:

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

The administration of RIVA-NAPROXEN (naproxen) may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that RIVA-NAPROXEN therapy be temporarily discontinued 48 hours before adrenal function tests are performed.

The drug may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

ADVERSE REACTIONS

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

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.

The adverse reactions in controlled clinical trials in 960 patients with rheumatoid arthritis or osteoarthritis treated with the naproxen standard tablets are listed below:

(1) Denotes incidence of reported reaction between 3% and 9%.

(2) Denotes incidence of reported reactions between 1% and 3 %. Reactions occurring in less than 1% of the patients are unmarked.

Gastrointestinal: Heartburn (1), constipation (1), abdominal pain (1), nausea (1), diarrhea (2), dyspepsia (2), stomatitis (2), diverticulitis (2), gastrointestinal bleeding, hematemesis, melena, peptic ulceration with or without bleeding and/or perforation, vomiting, ulcerative stomatitis.

Central Nervous System: Headache (1), dizziness (1), drowsiness (1), light-headedness (2), vertigo (2), depression (2) and fatigue (2). Occasionally patients had to discontinue treatment because of the severity of some of these complaints (headache and dizziness). Other adverse effects were

inability to concentrate, malaise, myalgia, insomnia and cognitive dysfunction (i.e. decreased attention span, loss of short term memory, difficulty with calculations).

Dermatologic: Pruritus (1), ecchymoses (1), skin eruptions (1), sweating (2), purpura (2), alopecia, urticaria, skin rash, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, photosensitive dermatitis, exfoliative dermatitis, erythema nodosum.

Hepatic: Abnormal liver function tests, jaundice, cholestasis and hepatitis.

Cardiovascular: Dyspnea (1), peripheral edema (1), palpitations (2), congestive heart failure and vasculitis.

Renal: Glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, nephropathy and tubular necrosis.

Hematologic: Eosinophilia, granulocytopenia, leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia and hemolytic anemia.

Special Senses: Tinitus (1), hearing disturbances (2), hearing impairment and visual disturbances.

Others: Thirst (2), muscle weakness, anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever), angioneurotic edema, hyperglycemia, hypoglycemia, hematuria and eosinophilic pneumonitis.

The adverse reactions reported on both the standard tablets and the SR tablets were similar.

The following additional adverse events liave also been reported in the literature with naproxen:

Gastrointestinal: nonpeptic gastrointestinal ulceration, pancreatitis, colitis, esophagitis.

Renal: hyperkalemia, renal disease, renal failure, renal papillary necrosis, raised serum creatinine.

Central nervous system: aseptic meningitis, convulsions, dream abnormalities.

Dermatologic: fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythmateous, photosensitivity reactions including rare cases resembling porphyria cutanea tarda ("pseudoporphyria") or epidermolysis bullosa.

Cardiovascular: hypertension, pulmonary edema.

Respiratory: asthma.

Special senses: corneal opacity, papillitis, retrobulbar optic neuritis, and papilledema.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Significant overdosage may be characterized by drowsiness, dizziness, disorientation, heartburn, indigestion, epigastric pain, abdominal discomfort, nausea, vomiting, transient alterations in liver function, hypothrombinemia, renal dysfunction, metabolic acidosis and apnea. A few patients have experienced convulsions, but it is not clear whether or not these were naproxen related . No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion for three to seven days of doses up to 3,000 mg of naproxen. One patient ingested a single dose of 25g of naproxen and experienced mild nausea and indigestion. 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.

Should a patient ingest a large number of RIVA-NAPROXEN (naproxen) tablets, the stomach may be emptied and usual supportive measures employed. Animal studies suggest that the prompt administration of 50-100 g of activated charcoal as an aqueous slurry over 15 minutes within 2 hours of the overdose would tend to reduce markedly the absorption of the drug. In dogs 0.5 g/kg of charcoal was effective in reducing the plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. However, hemodialysis may still be appropriate in the management of renal failure.

DOSAGE AND ADMINISTRATION

Adult:

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis

Oral: The usual total daily dosage for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis is 500 mg a day in divided doses. It may be increased gradually to 750 or 1000 mg or decreased depending on the patient's response.

Studies have not shown any clinically significant benefit in using doses higher than 1000 mg/day. In patients who tolerate lower doses of naproxen well and who exhibit only a partial response to 1000 mg/day, the dose may be increased to 1500 mg/day for limited periods.

Experience with 1500 mg/day naproxen is limited to using the standard tablets. RIVA-NAPROXEN (naproxen) tablets should be swallowed with food or milk.

When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk (see Adverse Reactions).

In addition, patients on 1500 mg/day need to be followed closely for the development of any adverse events.

During long term administration the dose of RIVA-NAPROXEN may be adjusted up or down depending on the clinical response of the patient. A lower dose may suffice for long term administration.

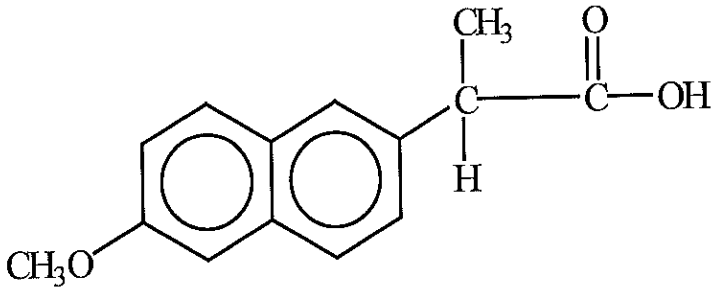
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Naproxen

Chemical Name: (+)–6–methoxy–α–methyl–2–naphthaleneacetic acid

Structural Formula:



Molecular Formula: $C_{14}H_{14}O_3$ Molecular Weight: 230.27

Description: Naproxen is a white or almost white, crystalline powder. It is insoluble in water but is soluble in organic solvents such as ethanol, methanol, chloroform and ether. It has a melting point of about 156°C.

Stability and storage recommendations: Store between 15°–30°C. Unit dose strips should be stored between 15°–25°C and protected from high humidity.

...on medicinal ingredients:

RIVA-NAPROXEN Tablets contain: Sodium starch glycolate, D&C yellow #10 lake 15-20% (HT), FD&C yellow #6 lake 15-18% (HT), FD&C blue #1 lake 11-13% (HT), microcrystalline cellulose, sodium lauryl sulphate, povidone, colloidal silicon dioxide, magnesium stearate.

AVAILABILITY OF DOSAGE FORMS

RIVA-NAPROXEN (naproxen) is supplied as:

250 mg	Yellow, football shaped, unscored tablet engraved with "Riva" on one side, "250" on the other contains 250 mg of naproxen. Bottles of 100, 500 and 1000 tablets, and in boxes of 100 (as unit dose strips).
375 mg	Peach coloured, capsule shaped tablet, engraved "R|R" on the scored side, "375" on the other contains 375 mg of naproxen. Bottles of 100 and 500 tablets, and in boxes of 100 (as unit dose strips).
500 mg	Yellow coloured, capsule shaped, engraved "R|R" on the scored side, "500" on reverse containing 500 mg of naproxen. Bottles of 100 and 500 tablets, and in boxes of 100 (as unit dose strips).

INFORMATION FOR THE PATIENT

HOW TO MAKE RIVA-NAPROXEN WORK BEST FOR YOU

Your doctor has decided that RIVA-NAPROXEN (naproxen) is the best treatment for you. You should take RIVA-NAPROXEN only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly (>65 years) patient.

Be sure to take RIVA-NAPROXEN regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

RIVA-NAPROXEN does not cure arthritis, but it promotes suppression of the inflammation and the tissue damaging effects resulting from this inflammation. This medicine will help you only as long as you continue to take it.

If you have any questions after reading this information leaflet, be sure to ask your doctor or pharmacist.

./HAT IS RIVA-NAPROXEN?

RIVA-NAPROXEN is the product name for naproxen, a medicine used to relieve the pain and inflammation associated with arthritis. It belongs to a family of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-prostaglandin drugs.

WHAT DOES RIVA-NAPROXEN LOOK LIKE?

RIVA-NAPROXEN is available in easy to swallow tablets.

Your doctor has chosen the strength (dose) that he or she thinks will be most effective in relieving your condition, based on experience with similar medical problems.

HOW DOES RIVA-NAPROXEN WORK?

Conditions like yours are usually associated with three symptoms: pain, inflammation, and/or stiffness. Research shows that RIVA-NAPROXEN works by reducing the production of certain substances (called prostaglandins) that the body normally produces to help control such functions as muscle contraction, inflammation, and numerous other body processes.

Clinical studies indicate that when prostaglandin levels are reduced, the intensity of pain, stiffness, and inflammation is reduced as well.

HOW SHOULD YOU TAKE RIVA-NAPROXEN TO MAKE IT WORK BEST FOR YOU?

Usually RIVA-NAPROXEN tablets are prescribed to be taken twice a day. It doesn't need to be taken more often than that. You don't have to carry your medication with you everywhere - just take 1 dose in the morning and 1 dose in the evening. For the most relief, take your RIVA-NAPROXEN at the same time each day.

It's important to keep taking RIVA-NAPROXEN even after you start to feel better. This helps to keep your pain, tenderness, and stiffness under control.

STOMACH UPSET IS ONE OF THE COMMON PROBLEMS WITH NSAIDs:

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

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking RIVA-NAPROXEN unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medicine is not causing unwanted effects.

IMPORTANT! Your doctor may give you different instructions better suited to your specific needs. If you need more information about how to take RIVA-NAPROXEN properly, double-check with your doctor or pharmacist.

ALWAYS REMEMBER

THE RISKS OF TAKING THIS MEDICATION MUST BE WEIGHED AGAINST THE BENEFITS IT WILL HAVE

BEFORE TAKING THIS MEDICATION TELL YOUR DOCTOR AND PHARMACIST IF YOU:

- or a family member are allergic to or have had a reaction to RIVA-NAPROXEN, naproxen sodium, or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);

- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);

- have a history of stomach upset, ulcers, liver or kidney diseases;

- have blood or urine abnormalities:

- have high blood pressure;

have diabetes;

- are on any special diet, such as a low-sodium or low-sugar diet.

- are pregnant or intend to become pregnant while taking this medication;

- are breast feeding or intend to breast feed while taking this medication as this drug does pass into the milk of nursing women;

- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medications, blood thinners, corticosteroids, methotrexate, cyclosporine, lithium, phenytoin;

- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

WHILE TAKING THIS MEDICATION:

- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;

- some NSAIDs may cause drowsiness or fatigue in some people taking them. Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;

check with your doctor if you are not getting any relief of your arthritis or if any problems develop;

- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications;

- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;

- check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;

- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your doctor;

- check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;

YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL

DOES RIVA-NAPROXEN HAVE SIDE EFFECTS?

Along with its beneficial effects, RIVA-NAPROXEN, like ASA and other NSAID drugs, may cause some undesirable reactions, especially when used for a long time or in large doses. Naproxen has been prescribed for over 10,000,000 people worldwide in the last ten years. In most patients it has been well tolerated so the chances are that you will tolerate it well too. Side effects are significantly less than those occurring with acetylsalicylic acid in doses used to treat arthritis.

Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects.

Although not all of these side effects are common, when they do occur, they may require medical attention.

Contact your doctor immediately if you experience any of these symptoms:

- bloody or black tarry stools;
- shortness of breath wheezing, any trouble in breathing or tightness in the chest;
- skin rash, hives or swelling, itching;

- vomiting or persistent indigestion, nausea, stomach pain or diarrhea;
- yellow discoloration of the skin or eyes:
- any change in the amount or colour of your urine (dark red or brown);
- any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- malaise, fatigue, loss of appetite;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;
- hearing problems.

Other effects that have been reported infrequently include headache, drowsiness and ringing in the ears. These reactions usually do not pose a serious problem, and most people can continue treatment. More rarely, blood disorders have occurred. Almost all of the side effects experienced with RIVA-NAPROXEN stop when the medication is stopped.

STORAGE

RIVA-NAPROXEN tablets: Store between 15°–30°C. Unit dose strips should be stored between 15°–25°C and protected from high humidity.

RIVA-NAPROXEN SHOULD NOT BE USED IN CHILDREN UNDER THE AGE OF TWO YEARS OF AGE AS THE SAFETY AND EFFECTIVENESS IN THIS AGE GROUP HAS NOT BEEN ESTABLISHED.

RIVA-NAPROXEN SR HAS NOT BEEN STUDIED IN SUBJECTS UNDER THE AGE OF 18.

DO NOT KEEP OUTDATED MEDICINE OF MEDICINE NO LONGER NEEDED.

KEEP OUT OF THE REACH OF CHILDREN.

THIS MEDICATION HAS BEEN PRESCIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE IT TO ANYONE ELSE.

IF YOU REQUIRE MORE INFORMATION ON THIS DRUG, CONSULT YOUR DOCTOR OR PHARMACIST.

PHARMACOLOGY

Animal:

Naproxen has been shown to possess marked anti–inflammatory, analgesic and antipyretic activity as assessed by a variety of animal test procedures.

Anti–Inflammatory Activity:

In the rat paw edema assay, naproxen was more potent than phenylbutazone and acetylsalicylic acid, and slightly less potent than indomethacin.

In the rat granuloma assay, naproxen was more active than phenylbutazone and less active than indomethacin.

Analgesic Activity:

In a mouse analgesic assay using phenylquinone for pain induction, naproxen was more active than phenylbutazone and acetylsalicylic acid, and less active than indomethacin. Parallel comparative analgesic studies were done in rats with yeast–induced paw edema.

In these assays, naproxen had a higher relative potency than phenylbutazone and acetylsalicylic acid, but lower relative potency when compared to indomethacin.

Antipyretic Activity:

As an antipyretic in the rat using yeast–induced fever, naproxen was about as active as indomethacin, but more active than phenylbutazone and acetylsalicylic acid.

The comparative absorption, distribution metabolism and excretion of naproxen was studied in several species, including man. Naproxen was found to be rapidly absorbed in all species and, once in the blood was eliminated with half–lives ranging from 2 to 35 hours. Estimated volumes of distribution indicated that a large fraction of the drug is held in the blood, much like salicylates are. Virtually all of the drug present in the blood of humans was determined to be unchanged naproxen, while the rat and the monkey showed minor amounts of transformation products. With the exception of the dog, all species excreted naproxen and its metabolic transformation products predominantly in the urine. In the dog the preferred route was fecal.

Studies by Tomlinson et al have shown that naproxen can inhibit the synthesis of prostaglandin E_2 from arachidonic acid by bovine seminal vesicle microsomes. Naproxen, therefore, appears to act at least in part in a manner similar to other anti–inflammatory agents which block prostaglandin biosynthesis.

Human Metabolic Studies:

The plasma-level response to oral naproxen doses ranging up to 900 mg twice daily was studied in normal subjects. Experiments with tritium labelled naproxen showed that there was no difference in the fraction of ingested drug excreted in the stools whether the dose was 250 mg or 900 mg , thus eliminating the possibility that this effect was a result of incomplete absorption. Accelerated renal clearance at high doses because of diproportionate increases in the amount of unbound drug appeared to be the most likely explanation for the plateau effect.

In patients treated with maintenance dialysis for terminal renal failure, serum level studies indicated that the metabolite 6-0-desmethyl naproxen is dialysed, whilst naproxen is not. No accumulation of naproxen was found although serum levels of the metabolite increased.

Effect of Naproxen on Acetylsalicylic Acid–Induced Gastrointestinal Bleeding:

A small group of normal subjects demonstrating acetylsalicylic acid–induced gastrointestinal bleeding were switched directly at random to either naproxen or placebo. The amount of blood loss decreased quickly to normal with placebo and near normal with naproxen in the first week. In the second week after discontinuing acetylsalicylic acid, there was no statistical difference between naproxen and placebo.

TOXICOLOGY

Acute Animal Toxicity

The oral LD_{50} values for naproxen are as follows:

Hamster	4110 mg/kg
Rats	543 mg/kg
Dogs	>1000 mg/kg
Mice	1234 mg/kg

Subacute and Chronic Oral Toxicity

In subacute and chronic oral studies with naproxen in a variety of species, the principal pathologic effect was gastrointestinal irritation and ulceration. The lesions seen were predominantly in the small intestine and ranged from hyperemia to perforation and peritonitis.

Nephropathy was seen occasionally in rats, mice, rabbits at high-dose levels of naproxen, but not in rhesus monkeys or miniature pigs. In the affected species the pathologic changes occurred in the cortex and papilla. Some rats examined 14 days after single oral doses of 230 mg/kg or more of naproxen evidenced necrotic areas of cortical and papillary tissue. Tubular dilation (ectasia) occurred in rabbits dosed orally for 14 days with 200 mg/kg/day or more of naproxen. An examination of unfixed renal tissue from rabbits so treated was conducted and revealed the presence of diffraction patterns similar to that of crystalline naproxen. This suggests that the ectasia observed was a physical response to deposition of excreted naproxen within the tubules.

In mice given oral doses of 120 mg/kg/day or more of naproxen for 6 months, the kidneys were characterized by a low but non-dosage related incidence of cortical sclerosis and papillary tip necrosis. Chronic administration of high doses of naproxen to mice appears to be associated with exacerbation of spontaneous murine nephropathy.

A wide variation in susceptibility to gastrointestinal lesions from administration of naproxen was evident in the various species tested. For example, 30 mg/kg/day was tolerated well by rats for 90 days, but the same dose was ulcerogenic when administered for 6 months. Rhesus monkeys and miniature swine exhibited no significant pathology when dosed with naproxen at 43 mg/kg/day for

J days. This dose of naproxen was also tolerated by miniature swine without obvious evidence of adverse effects when administered daily for 1 year. In rhesus monkeys doses as high as 120 mg/kg/day administered b.i.d. for 6 months produced no clinical or histopathological evidence of gastrointestinal irritation although occult blood in the feees occurred more frequently in these animals as compared to controls. In rabbits the maximum tolerated repeated oral dose is 200 mg/kg/day. Mice tolerated oral daily doses of 240 mg/kg/day for 6 months. In both rabbits and mice, gastrointestinal and renal toxicity was reported at these dose levels. In dogs, on the other hand, 5.0 mg/kg/day approaches the maximum tolerated dose. This peculiar canine susceptibility to gastrointestinal effects of non-steroidal anti-inflammatory agents has also been shown with indomethicin and ibuprofen. In dogs, naproxen exhibits a considerably longer plasma half-life than it does in rats, guinea pigs, miniature swine, monkeys and man. The same observation has been made with ibuprofen in dogs compared to rats and man. In addition in the species listed, only the dog excretes significant amounts of administered naproxen in the feces (50%). in the rat, guinea pigs, miniature swine, monkeys and man, 86-94% of the administered drug is excreted in the urine. The suggested enterohepatic circulation of naproxen in the dog (as judged by the fecal excretion) may be a major factor in the susceptibility of the dog to gastrointestinal irritation by this compound.

Pathologic changes in the spleen and mesenteric lymph nodes as well as peritoneal inflammation and adhesions were considered to be clearly secondary to the effects of high doses of naproxen on the garointestinal tract. Moderate weight loss of the male secondary sex glands occurred in some studies in naproxen-treated rats and dogs. Histopathologically the affected glands in some instances exhibited atrophic and/or hypoplastic changes characterized by decreased secretory material. A possible estrogenic action of naproxen as a causative factor seems highly unlikely since in standard

bioassay procedures the drug exhibited no estrogenic activity. Nevertheless, daily doses of naproxen as high as 30 mg/kg administered for 60 days before mating had no effect on fertility and reproductive performance of male rats. These results reflect the physiological integrity of the entire male reproductive apparatus after administration of naproxen throughout the spermatogenic cycle.

Effect on Induced Infections in Rabbits

To determine whether treatment with naproxen affects the ability of animals to respond to bacterial infection, rabbits were inoculated subcutaneously with Diplococcus pneumomae.

For 21 days before bacterial challenge and during a 2-week post-challenge period, the animals were dosed daily by gavage with 2, 10 or 20 mg/kg of naproxen. Clinical condition, morbidity, mortality, gross and histopathologic changes were evaluated. There were no apparent effects of naproxen in altering the response of the animals to bacterial challenge.

TERATOLOGY

In teratology studies, no skeletal or visceral anomalies or pathologic changes were induced in the fetuses of pregnant rats and rabbits treated during organogenesis with daily oral doses of naproxen up to 20 mg/kg. In these studies there were also no significant differences from controls in the number of live fetuses, resorptions, fetal weights or ano-genital distances.

REPRODUCTIVE STUDIES

Daily oral administration of 15, 30 or 60 mg/kg of naproxen to female rabbits from 2 weeks before mating until day 20 of pregnancy did not affect fertility, gestation or the numbers of live fetuses.

In a peri- and post-natal study in rats, oral doses of naproxen up to 20 mg/kg administered daily during the last part of pregnancy through weaning did not result in adverse effects in viability of pups, lactation index, sex ratio or weight gain of offspring. However, there was a slight increase in gestation length at the 10 and 20 mg/kg dose levels; and, at the 10 mg/kg dose level, there was a significant increase in stillbirths.

Naproxen at daily oral doses of 12, 36 or 108 mg/kg to female mice from 2 weeks before mating until weaning of the pups did not cause changes in length of gestation, number of live pups born, average pup weight at 0, 4, 7, 14 or 21 days, or sex distribution. The fertility index, gestation index and 4 day viability index were similar for mice from the control and treated groups. The 21 day survival and lactation indexes were decreased for mice from the group fed 108 mg/kg/day of naproxen but not for mice given 12 or 36 mg/kg/day. Most of this change was due to maternal mortality in the high dose group.

Recent evidence suggests that inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory compounds may be related to decreased uterine contractibility. Thus, the onset of labor in a rat model system can be delayed with naproxen administration without causing maternal or fetal deaths in excess of that seen in controls. Since it has been shown that Naproxen inhibits

prostaglandin synthesis in vitro, it has been suggested that the effects of naproxen on uterine contractility are mediated through that mechanism.

Maternal and fetal deaths seen in naproxen-treated rats were, therefore, apparently related to dysticia rather than to a direct toxic effect of the compound. Naproxen is not unique in this regard since comparable results were obtained in the rat with other commonly used non-steroidal anti-inflammatory agents.

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