PRODUCT MONOGRAPH

RIVA-NAPROXEN SODIUM

275 mg Tablets

RIVA-NAPROXEN SODIUM DS

550 mg Tablets

(Naproxen sodium, USP)

Analgesic, Anti-inflammatory Agent

Laboratoire Riva Inc.
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Date of Preparation:

August 30, 1999

Control Number: 062731

PRODUCT MONOGRAPH

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275 mg Tablets

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PHARMACOLOGICAL CLASSIFICATION

Analgesic, Anti–inflammatory Agent

ACTION AND CLINICAL PHARMACOLOGY

RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS (naproxen sodium) are nonsteroidal agents that possess analgesic, anti-inflammatory and antipyretic properties. Naproxen sodium exhibits an anti-inflammatory effect in adrenalectomized animals which shows its action is not mediated through the pituitary-adrenal axis. Naproxen sodium inhibits prostaglandin synthetase, as do certain other nonsteroidal analgesic/anti-inflammatory agents; however, the exact mechanism of its anti-inflammatory and analgesic actions is not known. It is not a corticosteroid.

Daily administration of 1100 mg of naproxen sodium to normal volunteers caused significantly less gastric bleeding and erosion than 3250 mg of acetylsalicylic acid.

The analgesic effect of the recommended dosage of naproxen sodium was shown to be comparable to that observed using 650 mg of acetylsalicylic acid. Within one hour of administration the analgesic effect is obtained which can last at least 7 hours.

Pharmacokinetics

Naproxen sodium is freely soluble in water and is completely absorbed from the gastrointestinal tract. Within 20 minutes of administration detectable plasma levels are obtained, reaching their peak level in approximately one hour. It is extensively bound to plasma protein and has a plasma half-life of approximately 13 hours. Excretion is primarily via the urine with only 1% of the dose excreted in the faeces.

Bioavailability

A randomised comparative, two-way crossover bioavailability study was performed on RIVA-NAPROXEN Sodium 275 mg film coated tablets and Anaprox® 275 mg film coated tablets. Naproxen sodium tablets were administered as a single dose (2 x 275 mg RIVA-NAPROXEN Sodium versus 2 x 275 mg Anaprox® tablets) with 240 mL water following an overnight fast. The pharmacokinetic plasma data (mean ± standard deviation) calculated for the RIVA-NAPROXEN Sodium and Anaprox® formulations is tabulated below:

	Riva-Naproxen Sodium 2 x 275 mg	Anaprox® 2 x 275 mg
Area under the Curve: (ng-hours/mL); 0-48 hours	964.40 ± 221.51	1024.25 ± 202.34
Peak Concentration: Cmax (ng/mL)	88.12 ± 21.39	95.33 ± 15.87
Time of Peak Level: Tmax (hours)	0.92 ± 0.39	0.81 ± 0.24
Elimination half-life: t-1/2 (hours)	10.67 ± 2.55	10.37 ± 2.89
Elimination Rate Constant: Kel ($hour^{-1}$)	0.07 ± 0.02	0.07 ± 0.02

Statistical evaluation by analysis of variance (ANOVA) of 0 - 24 hour AUC, Cmax, t–1/2, Tmax and Kel showed no significant differences among the two formulations. Details of this comparative bioavailability study are available from Laboratoire Riva Inc. upon request.

When naproxen sodium is taken with food, the rate but not the extent of absorption of the drug is decreased.

INDICATIONS AND CLINICAL USE

RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS (naproxen sodium) are indicated for the relief of mild to moderately severe pain, accompanied by inflammation in conditions such as musculoskeletal trauma and post-dental extraction.

RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS are also indicated for the relief of pain associated with post-partum cramping and dysmenorrhea.

CONTRAINDICATIONS

1. Peptic ulcer or active inflammatory disease of the gastrointestinal system.

2. Known or suspected hypersensitivity to the drug. RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS (naproxen sodium) should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti–inflammatory agents. Fatal anaphylactic reactions have occurred in such individuals.

WARNINGS

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti–inflammatory drugs (NSAID's) including naproxen sodium.

RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS (naproxen sodium) 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. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Nonsteroidal anti-inflammatory agents, including naproxen sodium may cause bronchoconstriction or anaphylaxis especially in aspirin-sensitive asthmatics, especially those with the triad of aspirin-induced nasal polyps, allergies and asthma. Patients should therefore be questioned for any history of these effects including urticaria and hypotension associated with these agents before starting therapy. Treatment should be discontinued if such symptoms occur during therapy.

Use in Pregnant or Lactating Woman: The safety of naproxen sodium has not been established in these conditions and therefore the use of this drug is not recommended during pregnancy or lactation. Reproduction studies have been performed in rats, rabbits and mice. In rats, pregnancy was prolonged when naproxen sodium was given before the onset of labour; when it was given after the delivery process had begun, labour was protracted. Drugs of this class are also known to cause closure of the ductus arteriosus and thus affect the human foetal cardiovascular system. Use of naproxen sodium during late pregnancy should therefore be avoided. The naproxen anion readily crosses the placental barrier. It has been found in the milk of lactating woman at a concentration of approximately 1% of that found in the plasma.

Use in Elderly, Frail or Debilitated Patients: The incidence of gastrointestinal ulceration/bleeds due to naproxen administration is reportedly greater in patients 60 years or older. The unbound plasma fraction of naproxen may be increased in the elderly. If naproxen sodium is to be used in patients aged 60 and over, then careful monitoring of these patients is essential and it is recommended that the lowest effective dose be used. Caution is advised when high doses are required.

PRECAUTIONS

RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS (naproxen sodium) should not be used concomitantly with the related drug naproxen (RIVA-NAPROXEN) since they both circulate in plasma as the naproxen anion.

Gastrointestinal System:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS should be discontinued, and appropriate treatment instituted and the patient closely monitored.

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 continuation of RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS therapy when and if these adverse reactions appear. Anaemia secondary to gastrointestinal tract toxicity can occur, therefore periodic haemoglobin estimations are advised.

Renal Function:

RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS should be used very cautiously in patients with significantly impaired renal function since naproxen and its metabolites are eliminated from the body to a large extent by urinary excretion via glomerular filtration. Monitoring of serum creatinine and/or creatinine clearance is advised in these patients. A reduction in daily dosage should also be anticipated to avoid the possibility of excessive drug accumulation. Caution should be used if the drug is given to patients having baseline creatinine clearance less than 20 mL/minute. Mild elevations in BUN have developed in a few patients during clinical trials, the significance of which is unknown. In humans, two renal effects of greatest significance associated with nonsteroidal anti-inflammatory agents are: (a) acute

interstitial nephritis with haematuria, proteinuria and sometimes associated with nephrotic syndrome and (b) prostaglandin-dependent, reversible renal insufficiency leading to reduction in renal blood flow or blood volume. Patients at greatest risk are those with impaired renal function, extracellular volume depletion, sodium restrictions, congestive heart failure, liver dysfunction (e.g. cirrhosis with ascites), systemic lupus erythematosus, diabetes mellitus, or those taking diuretics and elderly. Patients on long–term therapy with naproxen sodium, especially those in the high risk categories should have blood chemistry and kidney function tests monitored periodically. If renal function deterioration commences, RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS administration should be stopped. Long term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology.

Hepatic Function:

As with other nonsteroidal anti–inflammatory drugs, borderline elevations of one or more liver tests may occur. 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 while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal 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 this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance:

Fluid retention and oedema have been observed in patients treated with naproxen sodium. 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. RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With NSAID treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such as diabetus mellitus or renal failure; elderly patients; and patients receiving concomitant therapy and other beta adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics.

Serum electrolytes should be monitored periodically during long–term therapy, especially in those patients at risk.

There is approximately 25 mg of sodium in each RIVA-NAPROXEN SODIUM tablet and 50 mg of sodium in RIVA-NAPROXEN SODIUM DS tablets . This should be considered in patients whose overall intake of sodium must be markedly restricted.

Although sodium retention has not been reported in metabolic studies, patients with questionable or compromised cardiac function may possibly be at a greater risk when taking RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS.

Haematology:

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

Blood dyscrasias associated with the use of nonsteroidal anti–inflammatory drugs are rare, but could be with severe consequences. Because abnormalities of bone marrow function have occurred, patients being treated with naproxen sodium should have periodic evaluations of their haemopoietic system.

Infection:

In common with other anti–inflammatory drugs, RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN DS may mask the usual signs of infection.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of naproxen sodium and other nonsteroidal anti–inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Central Nervous System:

Patients following therapy with naproxen sodium have reported headache, drowsiness, dizziness or light-headedness. Patients should be cautioned against operating machinery or motor vehicles if they are experiencing these symptoms (see ADVERSE EFFECTS).

Hypersensitivity Reactions:

Hive like swellings on the face, eyelids, mouth, lips or tongue, shortness of breath, troubled breathing, wheezing or tightness in the chest may occur with the use of RIVA-NAPROXEN SODIUM. If such symptoms develop this drug should be discontinued.

Use in Children:

RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS are not recommended for uses in children under 16 years of age because the safety and dose schedule have not been established in this age group.

Drug Interactions:

It has been shown through *in vitro* studies that naproxen sodium may displace other drugs that are albumin-bound from their binding sites because of its affinity for protein. This may consequently lead to drug interactions. Theoretically RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS can likewise be displaced. Short term controlled studies have thus far failed to show that naproxen sodium significantly affects prothrombin times when administered to individuals concomitantly receiving coumarin-type anticoagulants.

Since interactions have been seen with other nonsteroidal anti-inflammatory agents, caution is advised. Similarly, patients receiving RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity. Concurrent administration of probenecid increases naproxen plasma levels and significantly extends its plasma half-life.

Antidiabetic Agents: Concurrent use of naproxen sodium may increase the hypoglycaemic effect because prostaglandins are directly involved in regulatory mechanisms of glucose metabolism and possibly through displacement of the oral antidiabetics from serum proteins. Dosage adjustments may be necessary. Glipizide and glyburide, due to their non-ionic binding characteristics, may not be affected as much as other oral antidiabetic agents; however, caution with concurrent use is recommended.

Antihypertensives or Diuretics: Concurrent use with naproxen sodium may decrease the diuretic, natriuretic and antihypertensive effects of diuretics (e.g. furosemide). Concurrent use may also increase the risk of renal failure. The antihypertensive effects of propranolol and other beta blockers may also be reduced.

Anti-inflammatory Analgesics: The use of RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS in conjunction with acetylsalicylic acid or another nonsteroidal anti-inflammatory agent is not recommended since data is not available demonstrating that the combination produces greater improvement than that achieved with either drug alone, and the potential for adverse reactions is increased.

Lithium: Nonsteroidal anti-inflammatory agents, including naproxen, have been reported to increase steady state plasma lithium levels. When initiating, adjusting and discontinuing RIVA-NAPROXEN SODIUM or RIVA-NAPROXEN SODIUM DS, it is recommended that plasma lithium levels be monitored.

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

Methotrexate: Naproxen and other nonsteroidal anti-inflammatory agents have been reported to reduce the tubular secretion of methotrexate in animals with possible potentiation of its toxicity.

Food or Antacids: The rate of absorption of naproxen sodium is not adversely influenced by the presence of food. Concurrent administration of antacids alters the rate of absorption of naproxen sodium.

Laboratory Tests:

Naproxen sodium decreases platelet aggregation and prolongs bleeding time. When determining bleeding times, this effect should be considered.

Haemoglobin values should be determined frequently in patients having initial values of 10 grams or less and who are on long-term therapy.

RIVA-NAPROXEN SODIUM and RIVA-NAPROXEN SODIUM DS (naproxen sodium) may interfere with some urinary assays of 5-hydroxy indolacetic acid (5HIAA).

The administration of naproxen sodium may result in increased urinary values of 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 SODIUM and RIVA-NAPROXEN SODIUM DS therapy be temporarily discontinued 48 hours before adrenal function tests are performed.

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 on occasion, particularly in the elderly.

The following adverse reactions listed by system have been reported with approximate incidences when available:

Gastrointestinal:

Abdominal or stomach pain or discomfort (3-9%), heartburn or indigestion (3-9%), constipation (3-9%), nausea (3-9%), diarrhoea (3-9%), stomatitis (3-9%), diverticulitis (3-9%). Less frequently occurring adverse reactions include vomiting, anorexia, flatulence, melena and haematemesis. More serious adverse reactions may include haemorrhage, GI bleeding, ulcer formation and perforation. Although a causal relationship has not been directly determined, nonsteroidal anti-inflammatory agents may contribute to the formation of oesophageal stricture in patients with gastroesophageal reflux.

Central Nervous System:

Headache (3-9%), drowsiness (3-9%) dizziness or light-headedness (3-9%). Adverse CNS reactions occurring less frequently include vertigo, inability to concentrate, mental depression, nervousness, irritability, fatigue, malaise, myalgia, insomnia, and cognitive dysfunction (i.e. decreased attention span, loss of short–term memory, difficulty with calculations).

Dermatological:

Itching of skin (3-9%), ulcerative stomatitis (1-3%), skin eruptions (3-9%), ecchymoses (3-9%), sweating (1-3%), purpura (1-3%), exfoliative dermatitis, alopecia, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitive dermatitis, vasculitis and erythema nodosum.

Cardiovascular:

Fluid retention (3-9%), palpitations (1-3%), hypertension due to fluid retention, congestive heart failure, tachycardia and dyspnea.

Special Senses:

Patients receiving naproxen have experienced tinnitus (3–9%) and less frequently, other hearing or visual disturbances.

Haematological:

Adverse haematological effects of naproxen include thrombocytopenia, leukopenia, granulocytopenia and eosinophilia. Although a causal relationship to naproxen has not been established, agranulocytosis, aplastic anaemia and haemolytic anaemia have occurred in patients receiving the drug.

Renal:

Renal disease, glomerulonephritis, haematuria, interstitial nephritis, nephrotic syndrome, nephropathy, tubular necrosis and dysuria have been reported in patients receiving naproxen.

Hepatic:

Abnormal liver function tests, jaundice, cholestasis and hepatitis (which can be fatal) have been reported rarely in patients receiving naproxen.

Respiratory:

Eosinophilic pneumonitis.

Miscellaneous:

Thirst (3–9%), muscle weakness and cramps, anaphylactoid reactions, pyrexia, sore throat and menstrual disturbances have also been reported during naproxen therapy. Although a causal relationship to naproxen has not been established, hypoglycaemia, hyperglycaemia and angioedema have occurred rarely in patients receiving the drug.

SYMPTOMS AND TREATMENT OF OVERDOSE

Significant overdose may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. 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 25 g 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 naproxen was determined to be 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 tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. Animal studies suggest that the prompt administration of 5 grams activated charcoal would tend to reduce markedly the absorption of the drug. Since naproxen is highly protein bound, the plasma concentration is not decreased significantly by haemodialysis. However, haemodialysis may still be appropriate in the management of renal failure.

DOSAGE AND ADMINISTRATION

The recommended starting dose of RIVA-NAPROXEN SODIUM (naproxen sodium) for adults is two 275 mg tablets, followed by one 275 mg tablet every 6 to 8 hours, as required. The total daily dose should not exceed 5 tablets (1375 mg). Alternatively, one RIVA-NAPROXEN SODIUM DS tablet (550 mg) given twice daily may be used.

PATIENT INFORMATION LEAFLET

RIVA-NAPROXEN SODIUM

275 mg Tablets

RIVA-NAPROXEN SODIUM DS

550 mg Tablets

Naproxen Sodium, which has been prescribed to you by your doctor, is one of a large group of nonsteroidal anti–inflammatory drugs (NSAID's) and is used to relieve pain accompanied by inflammation in conditions such as musculoskeletal trauma and post–dental pain extraction. They are also indicated for the relief of pain associated with post–partum cramping and dysmenorrhea. Naproxen sodium works by reducing the production of certain substances (prostaglandins) that the body normally produces to help control such functions as muscle contraction, inflammation and numerous other body processes.

You should take naproxen sodium 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.

Be sure to take naproxen sodium regularly as prescribed. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhoea) occurs and continues, contact your doctor.

This medicine is available only with your doctor's prescription. Remember:

- This medicine has been prescribed for your current medical problem only. It must not be given to other people or used for other problems unless your doctor otherwise directs you.

PROPER USE OF THIS MEDICINE

Do not take ASA (acetylsalicylic acid), ASA–containing compounds or other drugs used to relieve symptoms of arthritis while taking naproxen sodium 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 medication is not causing unwanted effects.

SIDE EFFECTS OF THIS MEDICINE

Along with its beneficial effects, naproxen sodium, like other NSAID drugs, may cause some undesirable reactions. 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. Check with your doctor immediately if any of the following are noted:

- Bloody or black tarry stools.
- Shortness of breath, wheezing, any trouble in breathing or tightness in the chest.
- Skin rash, swelling, hives or itching.
- Indigestion, nausea, vomiting, stomach pain or diarrhoea.
- Yellow discoloration of the skin or eyes, with or without fatigue

- Any changes in the amount or colour of your urine (such as dark; red or brown).
- Swelling of the feet or lower legs.
- Blurred vision or any visual disturbance.
- Mental confusion, depression, dizziness, light-headedness.
- Hearing problems.

ALWAYS REMEMBER

Before taking this medication tell your doctor and pharmacists if you:

- Are allergic to naproxen sodium or other related medicines of the NSAID group such as acetylsalicylic acid, diflunisal, fenoprofen, flurbiprofen, diclofenac, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin.
- Have a history of stomach upset, ulcers, or liver or kidney disease.
- Are pregnant or intend to become pregnant while taking this medication.
- Are breast feeding.
- Are taking any other medication (either prescription or non-prescription).
- Have any other medical problem(s).

While taking this medication:

- Tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication.
- Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or light-headed after taking this medication. Tranquillisers, sleeping pills and certain antihistamines (anti–allergic) may increase the frequency and/or severity of these side effects.
- Check with your doctor if you are not getting any relief 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.
- Your regular medical check-ups are essential.
- If you want more information about this medicine, ask your doctor or pharmacist.

Laboratoire Riva Inc.
Blainville Canada

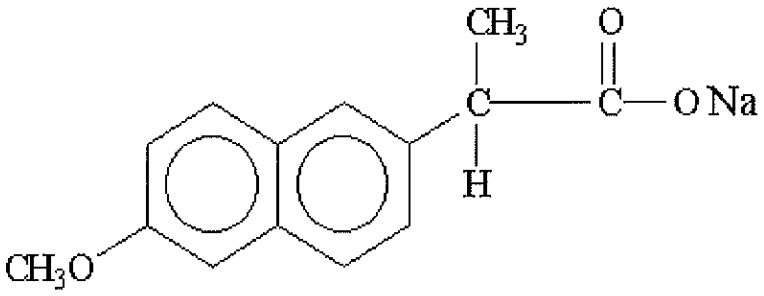
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Naproxen Sodium

Chemical Name: (–)–Sodium 6–methoxy–α–methyl–2–naphthalene–acetate.

Structural Formula:



Molecular Formula: $C_{14}H_{13}NaO_3$ Molecular Weight: 252.54

Description: Naproxen sodium is a white to creamy white, practically odourless crystalline powder. It is soluble in water and methanol; sparingly soluble in alcohol; very slightly soluble in acetone and practically insoluble in chloroform. Naproxen sodium melts at approximately 225°C with decomposition.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C – 30°C.

AVAILABILITY OF DOSAGE FORMS

RIVA-NAPROXEN SODIUM are available as blue film coated, engraved 'Riva-275' on one side tablets containing 275 mg of naproxen sodium. Available in bottles of 100 and 250 tablets.

RIVA-NAPROXEN SODIUM DS are available as film–coated, blue, oval–shaped with white cores, engraved 'R-DS-550' on one side tablets containing 550 mg of naproxen sodium. Available in bottles of 100 and 250 tablets

PHARMACOLOGY

Numerous pharmacological tests were conducted to assess the analgesic, antipyretic and anti-inflammatory activities of naproxen sodium. The reported results have shown that in man and animals, regardless of whether naproxen or naproxen sodium is administered, the circulating moiety is the same naproxen anion. The drug was active in all tests used to identify analgesic, anti-inflammatory and antipyretic activities where an inflammatory component was present with no discrepancies or exceptions evident.

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

Like ASA, phenylbutazone and other anti-inflammatory analgesics, naproxen sodium raised the pain threshold only in experimental pain states involving inflammation as

opposed to morphine, which raised the pain threshold in both inflamed and uninflamed states.

Antipyretic Activity

In rat studies using yeast-induced fever, naproxen had antipyretic activity similar to that of indomethacin but was more active than phenylbutazone and acetylsalicylic acid.

Anti-Inflammatory Activity

In various test systems, naproxen and naproxen sodium were slightly less active than indomethacin and more active than hydrocortisone, acetylsalicylic acid, phenylbutazone and mefenamic acid. The duration of anti-inflammatory action of naproxen appears to be relatively short based on anti-oedema in the rat. These findings however, may only b□e relevant to this species since metabolic half-life determination in man indicate a much longer duration of action.

Similar to other nonsteroidal anti-inflammatory agents, naproxen and naproxen sodium appear to act directly at inflamed tissue sites. Their activity is not mediated by corticosteroids. The compounds do not have thymolitic activity and they have reduced inflammation in adrenalectomized rats.

Naproxen sodium produced significant inhibition of granuloma tissue (cotton-pellet-test) over a relatively wide dose range (3-30 mg/kg/day), without affecting body weight or inducing other toxic manifestations.

Prostaglandin Synthesis Inhibition

The synthesis of prostaglandins □E_2 and $F_{2\alpha}$ from arachidonic acid by bovine seminal vesicle microsomes and pregnant rat uterine microsomes is inhibited by naproxen sodium. Suppression of PGE production in cultures of rheumatoid synovial

tissue also occurs and the drug inhibits arachidonate-induced foetal bone resorption *in vitro*. Delay of parturition observed with naproxen sodium administration, and other nonsteroidal anti-inflammatory agents might be explained by this inhibition of uterine prostaglandin biosynthesis. Prostaglandins are known to stimulate uterine smooth muscle contractions both *in vitro* and *in vivo*, thus playing an important role in initiating labour at term.

Naproxen sodium inhibited the biosynthesis of both $PGF_{2\alpha}$ and PGE_2 by pregnant rat uterine microsomes in a dose dependent manner. It was about 0.3 to 0.5 times as potent as indomethacin in this system. In contrast, it was 0.04 to 0.06 times as potent as indomethacin in inhibiting $PGF_{2\alpha}$ and PGE_2 synthesis by bull seminal vesicle microsomes.

Cardiovascular and Central Nervous System Effects

Naproxen sodium was almost inert in cardiovascular system studies and was found to have minimal CNS effects. CNS depressants such as phenobarbital, pentobarbital or chlordiazepoxide can control the effects of excessive amounts of naproxen sodium.

Reproductive System Effects

Naproxen had no demonstrable estrogenic, anti–estrogenic or androgenic effects. High toxic dose levels decreased pregnancies that appeared to be an indirect consequence of general toxicity rather than a true anti–fertility effect.

Animal Metabolism

The comparative absorption, distribution, metabolism and excretion of naproxen were studied in several species including rats, dogs, guinea pigs, rhesus monkeys and minipigs. Naproxen was found to be rapidly absorbed in all species and, once in the blood, was eliminated with plasma half–lives ranging from 2 hours in the rhesus monkey to 35 hours in the dog. Estimated volumes of distribution indicated that a

large fraction of the drug is held in the blood, much like salicylates are. From studies in laboratory animal assays, 6–desmethylnaproxen, the major metabolite of naproxen, was shown to have only very weak activity.

Human Metabolism

Naproxen is a weak acid and since most body fluids have a pH higher than its pKa, the drug molecules exist in these physiological fluids in the anionic form. Therefore, any difference between ingested doses of naproxen sodium and naproxen exist only in the stomach; in the dissolution rate and the absorption rate. Once absorbed, the distribution, metabolism and excretion of the two agents are identical.

Following I.V. administration, tritiated naproxen appears to be distributed mainly in the blood and is present there only as the unchanged drug. It is extensively bound to plasma protein and has a half-life of approximately 13 hours. The preferred route of excretion is via the urine with ony 1% of the dose excreted in the faeces. The drug is excreted similarly by both the male and the female. Following 14 days of continuous exposure to the drug, there was no indication of induction of metabolising enzymes. Naproxen sodium is freely soluble in water and is completely absorbed from the gastrointestinal tract. Significant plasma levels are obtained in patients within 20 minutes and the peak level in one hour.

Blood levels achieved in the human following oral administration were only slightly lower than after rapid intravenous injection.

Naproxen has a relatively small volume of distribution (approximately 10%) of the body weight in man that suggests naproxen has a relatively high affinity for the blood since a large fraction of the dose is held in the central circulatory system. The small volume of distribution is probably due to extensive plasma protein binding and the pH

partitioning effect which act together to restrict naproxen largely to the plasma compartment.

Human metabolism of naproxen as determined by analysis of the urinary radioactivity following a 100 mg intravenous dose was found to be relatively simple. The parent structure was altered only by removal of a 6 methoxy group and by conjugation of the acid function. Seventy percent of the ingested dose was eliminated as either unchanged naproxen (10%) or as conjugated naproxen (60%). This conjugated fraction was comprised of 40% naproxen glucuronide and 20% other conjugates including glycine and sulphate conjugates. Approximately 28% of the dose underwent 6-demethylation. As a consequence, 5% of the dose appeared in the urine as demethylated naproxen and 23% as conjugates of emethylated naproxen. The conjugates are further separable into 12% glucuronide and 11% other conjugates. The plasma-level response to oral naproxen doses ranging up to 900 mg twice daily was studied in normal subjects. 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. 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 disproportionate increases in the amount of unbound drug appeared to be the most likely explanation for the plateau effect. This self-regulating mechanism could be important in preventing high blood concentration of the drug with resulting increased toxicity.

TOXICOLOGY

Naproxen sodium is the sodium salt of naproxen. In various animal species, as in man, the circulating plasma entity is the same (naproxen anion) with oral administration of either naproxen sodium or naproxen. Therefore, for the purpose of evaluating systemic toxicity, studies carried out with either compound are interchangeable.

Acute Animal Toxicity:

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

Mice LD_{50} – 1234 mg/kg.

Rats LD_{50} – 543 mg/kg.

Dogs LD_{50} > 1000 mg/kg

Hamster LD_{50} – 4110 mg/kg

Subacute Toxicity:

Repeated dose administration trials (up to 3 months) were carried out in mice, rats, rabbits, dogs, minipigs and monkeys. Orally tolerated doses were about 200 mg/kg in rabbits, 30 mg/kg in rats and 50 mg/kg in mice. The dog was far more sensitive, while the monkey and to a lesser extent minipigs, was more resistant to the gastrointestinal tract irritant effects of naproxen. Vomiting complicated accurate oral dosing in dogs. In all of these studies the principal toxicity was related to gastrointestinal irritation of variable intensity. Changes in haematology and blood chemistry, such as elevation of WBC, extramedullary haematopoiesis, reduction in circulating RBC, Hct and Hgb, elevations in alkaline phosphatase and BUN, and gross and histological pathologic observations were also noted. These were similar to changes observed with other nonsteroidal anti-inflammatory drugs of the prostaglandin synthetase inhibition type. Some renal damage was signalled by the appearance of elevated BUN levels and proteinuria, which at autopsy was confirmed

as interstitial renal inflammation and nephritis. When it was topically applied to the eye for seven days, there was no increase in intraocular pressure.

Nephropathy was seen in rats, mice, rabbits and monkeys dosed with naproxen. In the affected species the pathologic changes occurred in the cortex and papillia. 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. Focal papillary degeneration in the kidney has been noted at chronic doses of 24 mg/kg/day. 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.

Chronic Toxicity:

In mice given oral doses of 120 mg/kg/day or more of naproxen for 6 months, the kidneys were characterised by a low but non dose–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.

Mice survived oral daily doses of 240 mg/kg/day for 6 months.

A two year rat study that included 100 animals/sex/level at 0, 8, 16 and 24 mg naproxen kg/day in the diet has been reported. Interim sacrifices were made at six and twelve months. With increasing dose gastrointestinal toxicity was increased, with females being more affected than males. This affected ability to gain weight, mortality, presence of abnormalities in haematology (reductions in Hg, Hct, elevated WBC) and clinical chemistry (elevated SGOT, BUN, and alkaline phosphatase).

Urinary changes (passing of more dilute urine and later greater volumes, some Haematuria) were indicative of some drug-induced renal damage. Periodic examination of the eye indicated no drug related toxicity. An analysis of *in vivo* palpated tissue masses and pathological examination of tissues at death or sacrifice indicated no increased potential for carcinogenicity that was attributable to the drug.

The principal dose related pathology noted again related to GI toxicity (ulceration, perforation to the tract and resulting peritonitis). Changes in haematology and blood chemistry, such as leukocytic infiltration of various organs, compensatory changes in the bone marrow and reticuloendothelial tissues, and extramedullary haematopoeisis in the spleen and liver were also noted. The kidney, another target organ, was more affected in males where papillary degeneration and necrosis were a notable finding. In females there was some retention of corpora lutea, which is another typical effect of prostaglandin inhibition. At 24 months a lower prostate and seminal vesicle weight was found in the 16 mg naproxen/kg/day group of male rats.

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 characterised 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.

Weight loss of the male secondary sex glands as a result of inanition is well documented, and intestinal irritation with the probability of decreased absorption may have contributed in this direction. 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.

Reproduction/Teratology/Fertility

In teratology studies no skeletal or visceral anomalies or pathologic changes were induced in the foetuses of pregnant rats and rabbits treated during organogenesis with daily oral doses of naproxen up to 20 mg/kg nor in mice similarly treated with 30 or 50 mg/kg. In these studies there were also no significant differences from controls in the number of live foetuses, resorption, foetal weights or ano-genital distances. In another mouse study no malformations were observed with administration of 60 or 120 mg/kg of naproxen although there was a slight reduction in the number of live foetuses in both dose groups and in foetal body weight in the high dose group.

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, of the number of live foetuses.

In a pre and postnatal 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, at the 10 and 20 mg/kg dose levels, there was a slight increase in gestation length; and, at the 10 mg/kg dose level, there was a significant increase in stillbirths.

Recent evidence, however, suggests that inhibition of prostaglandin synthesis by non-steroidal anti-flammatory compounds may be related to decreased uterine contractility. Thus, the onset of labour in a rat model system can be delayed with naproxen administration without causing maternal or foetal 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 foetal deaths seen in naproxen-treated rats were, therefore, apparently related to dystocia 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 (aspirin, indomethacin, mefenamic acid, and phenylbutazone). Similar results have been suggested in reports of other animal studies with mefenamic acid and ibuprofen.

In a fertility and reproductive study in mice, the dams were dosed daily with 12, 26 or 108 mg/kg from 14 days prior to mating through weaning. At the highest dose level, there was an increase in maternal deaths that were reflected in decreased 21 day survival and lactation indices. In a similar study in rats, daily doses were 2, 10 or 20 mg/kg from 14 days before mating through weaning. There were no differences between control and treated groups other than decreased survival to weaning that appeared due to poor maternal care in pups born to high dose dams. One mid and one high dose dam died during labour due to delayed parturition.

Effect on Induced Infections in Rabbits:

To determine whether treatment with naproxen affects the ability of animals to respond to bacterial infections, rabbits were inoculated subcutaneously with *Diplococcus pneumonia.* 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 conditions, 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.

Carcinogenicity:

A two year study in rats, and other studies, suggested that there is no added carcinogenicity in animals treated with naproxen.

Mutagenicity:

Mutagenicity studies were performed with naproxen using 5 strains of bacteria and one of yeast. The tests were carried out with and without mammalian microsomal activation. Naproxen was not mutagenic in any of these test systems.

REFERENCES

1. Bloomfield SS, Barden TP, Mitchel J. Naproxen, aspirin, and codeine in postpartum uterine pain. Clin Pharmacol Therap l977; 21:414-421

2. Brogden RN, Heel RC, Speight TM, Avery GS. Naproxen up to date: A review of its pharmacological properties and therapeutic efficacy and use in rheumatic diseases and pain stages. Drugs 1979;18:241-277.

3. Brogden RN, Pinder RM, Sawyer PR, Speight TM, Avery GS. Naproxen: A review of its pharmacological properties and therapeutic efficacy and use. Drugs 1975; 9:326-363.

4. Csapo AIO, Pulkkinen MO, Henzyl MR, Salau G. The delay of spontaneous labor by naproxen in the rat model. Prostaglandins 1973; 3:827-837.

5. Csapo AI, Pulkkinen MO, Henzyln MR. The effect of naproxen-sodium on the intrauterine pressure and menstrual pain of dysmenorrhaeic patients. Prostaglandins 1977; 13:103-199.

6. Dysmenorrhea and Prostaglandins. Proceedings of an international symposium in Helsinki, November 16-17, 1978. Acta Obstet Gynecol Scand Suppl 87 (1987).

7. Henzyl RM, Buttram V, Segre E, Bessler S. The treatment of dysmenorrhea with naproxen sodium. A report of two independent double-blind trials. Am J Obstet Gynecol 1977; 127:818-823.

8. Husby G, The Norwegian Multicenter study. Am J Med 81 (Suppl. 5B): 1986; 6-10.

9. Meisel AD. Clinical benefits and comparative safety of piroxicam: analysis of worldwide clinical trials data. Am J Med 1986; 81(Suppl. 5B):15-21.

10. Nadell J, Bruno J, Varady J, Segre E. Effects of naproxen and aspririn on bleeding time and platelet aggregation. J Clin. Pharmacol 1974; 14:186-182.

11. Roszkowski AP, Rooks WH, Tomolonis AJ, Miller LM. Anti-inflammatory analgesic properties of d-2-(6'-methoxy-2'-naphthyl-propionic acid (naproxen). J Pharmacol Exp Ther 197l; 1798:114-124.

12. Rugstad HE. The Norway study: Plasma concentrations, efficacy and adverse events.
Am J Med 1986; 81(Suppl. 5B):11-14

13. Runkel R, Chaplin M, Boost G, Segre E, Forchielli L. Absorption, distribution, metabolism, and excretion of naproxen in various laboratory animals and human subjects. J Pharm Sci 1972;
61:703-708.

14. Runkel R, Chaplin M, Sevelius H, Ortega E, Segre E. Pharmacokinetics of naproxen overdoses. Clin Pharmacol Ther 1976; 20:269-277.

15. Runkel R, Forchielli E, Sevelius H, Chaplin M, Segre E. Naproxen-metabolism excretion and comparative pharmcokinetics, Scan J Rheumatol 1973; 2:29-36.

16. Runkel R, Forchielli E, Sevelius H, Chaplin M, Segre E. Nonlinear plasma level response to high doses of naproxen. Clin Pharmacol Therap 1974; 15:261-266

17. Runkel R, Mroszczak E, Chaplin M, Sevelius H. Segre E. Naproxen-probenecid interaction. Clin Pharmacol Ther 1978; 24:706-713

18. Segre EJ. Naproxen sodium (Anaprox): Pharmacology pharmacokinetics and drug interactions. J Reprod Med 1980; 25-222-225.

19. Sevelius H, Runkel R, Segre E, Bloomfield SS. Bioavailability of naproxen sodium and its relationship to clinical analgesic effects. Br J Clin Pharmacol 1980; 10:259-263.

20. Thompson G, Collins J. Urinary metabolic profiles for choosing test animals for chronic toxicity studies: Appliction to naproxen. J Pharm Sci 1973; 62:937-941.

21. Tomlinson RV, Ringold HJ, Qureshi HC, Forchielli E. Relationship between inhibition of prostaglandin synthesis and drug efficacy: Support for the current therapy on mode of action of aspirin-like drugs. Biochem Biophys Res Comun 1972; 46:552-559.

22. U.S. FDA Summary Basis of Approval Documents for Anaprox (Naproxen Sodium) Syntex, File No. F80-22, 545.

23. U.S. FDA Summary Basis of Approval Documents for Naprosyn (Naproxen) Syntex, File No. F81-794.

24. RIVA-NAPROXEN Tablets Product Monograph, Laboratoire Riva Inc., Blainville, Canada, July 8, 1999.

25. A Comparative Bioavailability Study of Naparoxen Sodium Tablets in Human Volunteers, January 1986. Data on file at Laboratoire Riva Inc.

26. American Hospital Formulary Service Drug Information 87, ed McEnvoy Ek Bethesda MA 1987, p 924-946.

27. Drug information for the Health Care Provider, USP Di Vol k, Seventh Edition 1987, U.S. Pharmacopeial Convention In. Rockville MD, 1987, p. 296-314.

28. Advice for the Patient, USP DI, Vol II, Seventh Edition 1987, U.S. Pharmacopeial Convention Inc, Rockville, MD 1987, p. 128-131.

29. Health Protection Branch Information Letter on Nonsteroidal Anti-inflammatory Drugs, DD-33, dated August 21, 1985.

30. CPS 1991. Canadian Pharmaceutical Association, Ottawa, Ontario, Canada 1991; 67–8.

31. Anaprox® (naproxen sodium) product monograph, Syntex Inc., Mississauga, Ontario, August 14, 1990.