PRODUCT MONOGRAPH

NAPROSYN®
(naproxen)

250mg, 375mg, 500mg Film Coated Tablets

250 mg, 375 mg and 500 mg Enteric Coated (E) Tablets

750 mg and 1000 mg Sustained Release (SR) Tablets

25 mg/mL Suspension

500 mg Suppositories

An anti-inflammatory agent with analgesic

and

antipyretic properties.

Hoffmann-La Roche Limited
2455 Meadowpine Blvd.
Mississauga, Ontario
L5N 6L7

Date of Preparation:

May 10, 1995

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THERAPEUTIC CLASSIFICATION

An anti-inflammatory agent with
analgesic and antipyretic properties.

ACTION

Naproxen has demonstrated anti-inflammatory, analgesic and anti-pyretic 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.

From clinical trials it appears that Naprosyn E has reduced potential for severe complaints when compared to naproxen STD.

PHARMACOKINETICS:

Naproxen is rapidly and completely absorbed from the gastro-intestinal 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 time to reach peak plasma concentration following rectal administration of naproxen 500 mg suppository relative to the oral tablet was not significantly different. 0-24 hour areas under the plasma concentration versus time curves for the 500 mg dose of either naproxen tablets or suppository were similar. 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.

In children with rheumatic diseases aged between 5 to 16 years, naproxen reached peak plasma levels 2 to 4 hours following oral dosing and the mean plasma half-life was 11.5 to 14.1 hours. Naprosyn® Suspension was found to have similar bioavailability to the naproxen tablets in two single dose studies done in 24 healthy male volunteers. No clinically significant differences in tolerance were reported between the two dosage forms.

When naproxen is administered in the sustained release form (Naprosyn® SR), the peak plasma levels are delayed and the maximum plasma concentrations are reduced compared to those seen with standard release formulations of naproxen. The minimum plasma concentrations, at steady state, are equivalent between Naprosyn® SR given once a day and the corresponding standard dosage given twice a day. The peak to trough plasma concentration ratio of 2.2 and 2.6 observed with the standard tablet formulation (375 mg b.i.d. and 500 mg b.i.d. respectively) is reduced to 1.6 and 1.8 with the 750

and 1000 mg Naprosyn® SR tablets respectively, resulting in smaller fluctuations in plasma concentrations of naproxen with the Naprosyn® SR tablets.

The average T_{max} of naproxen in subjects receiving the 1000 mg SR tablet immediately after a high-fat meal did not differ significantly when compared to the fasting state (7.7 hours post-prandial; 9.7 hours fasting). The average C_{max} increased significantly from 63.1 μg/mL (fasting) to 86.1 μg/mL (post-prandial). This increase in C_{max} was still lower than that observed with the 1000 mg dose of standard Naprosyn® tablets. Based upon the 95% confidence interval, the AUC's were equivalent when the SR tablet was administered under fasting and non-fasting conditions.

A 28 day study of chromium - 51 - labeled red blood cell loss in feces was conducted with the 750 mg sustained release naproxen tablets in 20 patients. There was no statistically significant difference in red blood cell loss between patients 60 years of age or younger and those over 60.

Enteric-coated naproxen (Naprosyn E) is designed to be dispersed and dissolved in the small bowel rather than the stomach, so the absorption is delayed until the stomach is emptied. Naproxen enteric-coated tablets were bioequivalent to the standard 375 mg and 500 mg tablets, except for a substantially increased time to peak plasma concentration (T_{max}). The average maximum plasma concentration (C_{max}) following the 375 mg, 2 x 250 mg and 500 mg enteric-coated tablets were 47.9, 58.2 and 60.7 μg/ml, while the C_{max} following the 375 mg and 500 mg standard immediate release tablets were 46.6 and 63.1 μg/ml, respectively. The $T_{max's}$ were 4.5, 4.2 and 4.2 hr. for the respective enteric-coated formulations as compared to 2.3 and 2.6 hr. after standard naproxen tablets. At steady state (multiple dosing) naproxen enteric coated and naproxen STD were equivalent to each other with respect to C_{max}, C_{ave}, C_{max}/C_{ave}, 0-12 hr. AUC and half-life. In addition, fluctuation in plasma levels about C_{ave} were considerably less with naproxen EC as compared to naproxen STD (49.3% vs 85.3%). Administration of 500 mg enteric-coated naproxen tablets with food and antacid did not alter the extent of

absorption of naproxen as compared to the fasting condition. However, antacid treatment resulted in a higher C_{max} (70.7 vs 58.5 μg/ml) and earlier T_{max} (5.2 hr vs. 8.7 hr.) in comparison to the fasting condition. Relative to the fasting state, the average T_{max} was delayed following a high fat meal (5.6 - 8.7 hr. fasting, 9.2 - 10.8 hr. post-prandial) while the average C_{max} and AUC were bioequivalent.

INDICATIONS AND CLINICAL USES

Naprosyn® (naproxen) is indicated for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and juvenile rheumatoid arthritis.

CONTRAINDICATIONS

Naprosyn® (naproxen) is contraindicated in patients with active peptic ulcers or active inflammatory diseases of the gastro-intestinal tract. Naprosyn® is also contraindicated in patients who have shown hypersensitivity to it or to naproxen sodium. Since cross-sensitivity has been demonstrated, Naprosyn® should not be given to patients in whom acetylsalicylic acid or other non-steroidal anti-inflammatory drugs induce the syndrome of asthma, rhinitis or urticaria. Sometimes severe and occasionally fatal anaphylactoid reactions have occurred in such individuals.

Naprosyn® suppositories are contraindicated in children under 12 years of age. The suppositories are also contraindicated in patients with any inflammatory lesions of rectum or anus and in patients with recent history of rectal or anal bleeding.

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 Naprosyn®.

Naprosyn® 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 this drug 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.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

Use in pregnancy and lactating women:

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 inhibition of prostaglandin synthesis. 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. Naprosyn® (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

Naprosyn® (naproxen) should not be used concomitantly with the related drug Anaprox® (naproxen sodium) since they both circulate in plasma as the naproxen anion.

Gastro-intestinal system

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs Naprosyn® should be discontinued, an appropriate treatment instituted and 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 Naprosyn® therapy when and if these adverse reactions appear.

Naprosyn® suppositories should be given under close supervision in patients with any rectal or anal pathology (see contraindications).

Renal effects

As with other non-steroidal anti-inflammatory drugs, long-term administration of naproxen 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.

Naprosyn® and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. A reduction in daily dosage should be anticipated to avoid the possibility of excessive drug accumulation.

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.

Fluid 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.

Naproxen formulated as a suspension (25mg/mL) contains sodium chloride (20 mg/mL). This should be considered in patients whose overall intake of sodium must be restricted.

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 concomittant 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.

Hypersensitivity

Anaphylactoid reactions to naproxen or naproxen sodium, 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.

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.

Use in patients with impaired liver function

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. 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 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 this drug is to be used 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.

Hematology

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 Naprosyn® is administered.

Blood dyscrasias associated with the use of non-steroidal anti-inflammatory drugs are rare, 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 Naprosyn® (naproxen) may mask the usual signs of infection and the physician should be alert for development of infection in patients receiving Naprosyn®.

Ophthalmology

Because of adverse eye findings in animal studies with drugs of this class it is recommended that ophthalmic studies be carried out within a reasonable period of time after starting therapy and at periodic intervals thereafter if the drug is to be used for an

extended period of time.

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

Drug Interactions

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 bishydroxycoumarin or warfarin, the addition of Naprosyn® could prolong the prothrombin time. These patients should therefore be under careful observation. Similarly, patients receiving Naprosyn® and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations have also been reported.

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.

The rate of absorption of naproxen is altered by concomitant administration of antacids but is not adversely influenced by the presence of food. Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

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.

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 Naprosyn® (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 Naprosyn® 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 on occasion, particularly in the elderly.

The adverse reactions in controlled clinical trials in 960 patients with rheumatoid arthritis or osteoarthritis treated with the Naprosyn® (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.

In addition to the above, rectal burning (1) has been reported occasionally and rectal bleeding rarely, with the use of naproxen suppositories.

Central Nervous System: Headache (1), dizziness (1), drowsiness (1), light-heaedness (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).

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

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

Cardiovascular Reactions: 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: Tinnitus (1), hearing disturbances (2), and hearing impairment 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Significant overdosage may be characterized 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 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 Naprosyn® (naproxen) tablets, the stomach may be emptied and usual supportive measures employed. Animal studies suggest that the prompt administration of 5g of activated charcoal would tend to reduce markedly the absorption of the drug. In dogs 0.5g/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:

Oral: The usual total daily dosage for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis is 500 mg (20 mL, 4 teaspoons) a day in divided doses. It may be increased gradually to 750 or 1000 mg or decreased depending on the patient's response. Naprosyn tablets should be swallowed with food or milk.

Patients with rheumatoid arthritis or osteoarthritis maintained on a dose of 750 or 1000 mg/day in divided doses can be switched to a once daily dose of Naprosyn® SR (naproxen sustained release) 750 mg or 1000 mg respectively. The single daily dose of Naprosyn® SR should not be exceeded and can be administered in the morning or evening. Naprosyn® SR tablet should be swallowed whole.

Rectal: Naprosyn® suppositories (500 mg) can replace one of the oral doses in patients receiving 1000 mg of Naprosyn® daily.

Naprosyn® suppositories are not indicated in children under 12 years of age.

Juvenile Rheumatoid Arthritis: The recommended total daily dose is approximately 10 mg/kg in two divided doses at 12 hour intervals. The following table may be used as a guide:

Child's Weight	Dose
13 Kg (29 lbs.)	2.5 mL (1/2 tsp.) b.i.d.
25 Kg (55 lbs.)	5 mL (1 tsp.) b.i.d.
38 Kg (84 lbs.)	7.5 mL (1-1/2 tsp.) b.i.d.

Administration of Naprosyn® more frequently than twice daily is not necessary. Clinical experience has shown that steroids can often be decreased and sometimes eliminated when Naprosyn® is administered.

Bottles of Naprosyn® suspension should be shaken gently before use.

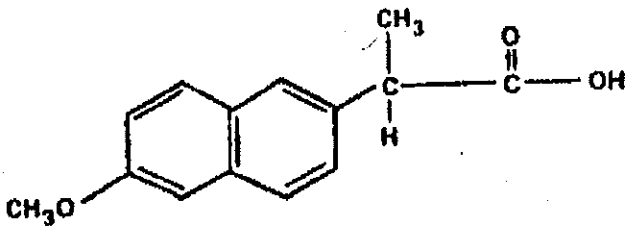
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name Naproxen

Chemical Name (+)-6-methoxy- alpha-methyl-2-naphthaleneacetic acid.

Structural Formula



Molecular Weight 230.27

Description Naproxen is an odorless white crystalline powder with a melting point of 152 - 158°C. It is highly lipid soluble, sparingly soluble in water at low pH and highly soluble in water at high pH.

Composition

Naprosyn Tablets:

Naprosyn (naproxen) tablets (250 mg, 375 mg and 500 mg) also contain starch, povidone, magnesium stearate and lactose as inactive ingredients. The coating suspension consist of hydroxypropyl methyl cellulose and propylene glycol. Naprosyn

250 mg and 500 mg tablets contain D & C Yellow #10 and F D & C Yellow #6 and Naprosyn 375 mg tablets contain F D & C Yellow #6 as colourants.

Naprosyn SR Tablets:

Naprosyn SR (naproxen sustained release) tablets (750 mg and 1000 mg) also contains hydroxypropyl methylcellulose and magnesium stearate as inactive ingredients and F D & C Yellow #6 as colourant.

Naprosyn E Tablets:

Naprosyn E (naproxen enteric coated) tablets (250 mg, 375 mg and 500 mg) also contains povidone, crosscarmellose sodium and magnesium stearate as inactive ingredients. The coating suspension consists of methacrylic acid copolymer, talc, sodium hydroxide and triethyl citrate. The green ink for printing Naprosyn E 375 mg contains D & C Yellow #10 aluminum lake and F D & C Blue #1 aluminum lake. The red ink for printing Naprosyn E 250 mg and 500 mg contains F D & C Red No. 40 aluminum lake, propylene glycol, n-butyl alcohol, titanium dioxide and SDA-3A alcohol.

Naprosyn Suspension:

Naprosyn (naproxen) suspension 25 mg/mL also contains magnesium aluminum silicate, fumaric acid, methylparaben, sucrose, sorbitol solution, sodium chloride, imitation pineapple flavour and imitation orange flavour as inactive ingredients and F D & C Yellow #6 as colourant.

Naprosyn Suppositories:

Naprosyn (naproxen) suppositories 500 mg also contains witepsol H15 as inactive ingredient.

Stability and Storage Recommendations:

Naprosyn tablets, Naprosyn SR tablets, Naprosyn E tablets and Naprosyn suppositories: Store at room temperature.

Naprosyn Suspension: Store at room temperature not exceeding 25°C, with protection from light.

AVAILABILITY OF DOSAGE FORMS

Naprosyn® is available as:

Tablets -	250 mg - oval, yellow tablets, engraved N on one side and SYNTEX on the other in bottles of 100 and 1000 tablets.
	375 mg - peach, scored, capsule-shaped tablets, engraved SYNTEX on one side in bottles of 100 and 500 tablets.
	500 mg - yellow, scored, capsule-shaped tablets, engraved SYNTEX on one side in bottles of 50 and 500 tablets.
Sustained Release Tablets	750 mg - peach oval-shaped tablet with SR-750 embossed on one side and SYNTEX on the other, in bottles of 100, 250 and 500 tablets.
	1000 mg - peach ellipsoid-shaped tablet with SR-1000 embossed on one side and SYNTEX on the other, in bottles of 50 and 250 tablets.

Enteric-Coated Tablets	250 mg - round biconvex, enteric-coated tablet with one side printed in red with stylized "N" and the other side with "E250". Available in bottles of 100 and 500 tablets.
	375 mg - modified capsule shaped, enteric coated tablet with one side printed in green with stylized "N" and the other side with "E375" Available in bottles of 100 and 500 tablets.
	500 mg - modified capsule shaped, enteric coated tablet with one side printed in red with stylized "N" and the other side with "E500" Available in bottles of 100 and 500 tablets.
Suspension -	Each 5 mL contains 125 mg of naproxen. Available in bottles of 500 mL.
Suppositories-	Each white opaque suppository contains 500 mg of naproxen. Available in boxes of 30, packed in polyethylene-lined white polyvinyl shells in perforated strips of 5 suppositories.

INFORMATION FOR THE PATIENT

HOW TO MAKE NAPROSYN® WORK BEST FOR YOU

Your doctor has decided that Naprosyn® (naproxen) is the best treatment for you. As you take your Naprosyn® tablets, remember that your chances of controlling your symptoms are greater if you cooperate fully with your doctor and try to become well informed about your condition.

This leaflet is not as thorough as the official Product Monograph on Naprosyn® (which your doctor or pharmacist has available), and is meant to supplement what your doctor has told you. Your doctor knows and understands your personal condition; be sure to follow your doctor's instructions carefully and read any materials he or she gives you. **If you have any questions after reading this information leaflet, be sure to ask your doctor.**

WHAT IS NAPROSYN®?

Naprosyn® 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 non-steroidal anti-inflammatory drugs (NSAIDs) or anti-prostaglandin drugs.

WHAT DOES NAPROSYN® LOOK LIKE?

Naprosyn® is available in easy to swallow, film-coated tablets, enteric coatedtablets and as sustained release tablets which allows once daily dosing. A liquid form (a suspension), which has an orange-pineapple flavour and a rectal suppository are also available.

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 NAPROSYN® WORK?

Conditions like yours are usually associated with three symptoms: pain, inflammation, and/or stiffness. Research shows that Naprosyn® 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 NAPROSYN® TO MAKE IT WORK BEST FOR YOU?

Usually Naprosyn® film coated tablets or suspension 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 one dose in the morning and one dose in the evening. The sustained release Naprosyn® SR tablets have been designed for convenient once daily dosing in the morning or evening. The maximum daily dose of Naprosyn® SR must not be exceeded and should be swallowed whole. For the most relief, take your Naprosyn® at the same time each day.

If Naprosyn® Suppositories have been prescribed, your Doctor or Pharmacist will explain how to use them.

It's important to keep taking Naprosyn® even after you start to feel better. This helps to keep your pain, tenderness, and stiffness under control. You should take Naprosyn® with food or milk.

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

HOW LONG DOES IT TAKE BEFORE NAPROSYN® BEGINS TO WORK?

Naprosyn® is completely absorbed into your system usually within two to four hours. Some people are able to feel improvement in their symptoms right away; for others, improvement may take up to two weeks. By the end of two weeks, if Naprosyn® does not seem to be helping you, tell your doctor. You may need a different dosage, or your doctor may want to prescribe another treatment program for you.

WILL THE AMOUNT OF NAPROSYN® YOU TAKE EVER CHANGE?

It might change. Your condition, as your doctor may have explained to you, has its ups and downs. The amount of pain, stiffness, and inflammation in your joints may vary from week to week. As time goes by, your doctor may decide that it is advisable to make adjustments in the dosage of Naprosyn® you are taking. He or she may suggest that you increase or decrease your medication according to how severe your symptoms are or how active you are.

Follow instructions; your doctor understands how to set the upper and lower dosage limits so that you get the greatest benefit from Naprosyn®.

DOES NAPROSYN® HAVE SIDE EFFECTS?

Any medication can cause side effects; this is true for acetylsalicylic acid (ASA) and all of the non-steroidal anti-inflammatory drugs that are used to treat conditions like yours. Naprosyn® 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.

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

Relatively common unwanted side effects of all non-steroidal anti-inflammatory drugs are heartburn, pain in the gut, nausea, constipation, and so forth. Remember to take Naprosyn® with meals or with a glass of milk to reduce discomfort of this type.

If you have a history of stomach upset, or if you have an ulcer, tell your doctor. All non-steroidal anti-inflammatory drugs may aggravate your problem and sometimes even cause bleeding, or ulcers in your stomach or intestines. These complications can sometimes be severe and occasional fatalities have been reported with all drugs of this class.

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, swelling, hives or itching;

. indigestion, nausea, vomiting, stomach pain or diarrhea;

. 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

Other effects that have been reported infrequently include headache, drowsiness, dizziness, depression, and ringing in the ears. These reactions usually do not pose a serious problem, and most people can continue treatment. More rarely, visual or hearing disturbances and blood disorders have occurred. **Contact your doctor if you experience any problems.** Almost all of the side-effects experienced with Naprosyn® stop when the medication is stopped.

The use of rectal suppositories has in some patients, caused a burning sensation in the rectum and rarely rectal bleeding.

If you are allergic to ASA or to any of the other non-steroidal anti-inflammatory drugs (e.g. diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid, tolmetin) used to treat arthritis or other muscle and joint conditions, **do not take Naprosyn®.** You may be allergic to it too. **Also, you should not take Naprosyn® if you are already taking Anaprox® (naproxen sodium), a related drug.**

ARE THERE ANY SPECIAL DO'S and DON'TS ABOUT TAKING NAPROSYN®?

DO tell your doctor and pharmacist about any other medications you take, both prescription and nonprescription. This is important because some drugs can interact with each other and produce undesirable effects.

DO tell your doctor if you have an ulcer, liver disease, kidney disease, or history of any stomach problems.

DO be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy, or light-headed after taking Naprosyn® (naproxen).

DO check with your doctor if:

- you are not getting relief

or

- you have any problems while taking Naprosyn®

DO tell your physician if you are pregnant or are planning to become pregnant.

DON'T take Naprosyn® if you are breast-feeding. The drug does pass into the milk of nursing women.

DON'T take Naprosyn® if you are allergic to it, or if you have had an allergic-type reaction to ASA or to any other drug used for pain relief or arthritis. DO check with your doctor.

DO cooperate with your doctor if he or she wants you to take certain lab tests to monitor the effectiveness of treatment or possible side effects.

PHARMACOLOGY

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 disproportionate 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 gastro-intestinal bleeding: A small group of patients 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 and 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 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 45 mg/kg/day for 30 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 feces 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 indomethacin 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 gastrointestinal 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.

Toxicity Studies with Suppositories

In a subacute study, naproxen suppositories (15 mg and 150 mg) were administered once daily for a period of 14 days to rabbits, 4 animals per dose. One male in the 15 mg group died on day 6 and another in the 150 mg group died on day 11. There was no morphological evidence of ulceration or perforation. Microscopic examination showed a slight to moderate enteritis.

Occasional diarrhea, mucoid-nasal discharge and/or distended abdomen were noted in some animals regardless of sex, or dosage.

Rhesus monkeys were administered naproxen suppositories 300 mg once a day for 14 days. Weight-gain was similar to the control group. Insertion of the suppository in some cases caused mechanical injury resulting in slight rectal bleeding. Some animals exhibited lesions of peritonitis with omental adhesions, others had inflammatory changes and perforation of the gut wall. These were considered to be related in part to the administration technique since both control and test animals were involved. However, inflammatory changes observed in the dosed animals were more frequent and severe.

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 pneumoniae. 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 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.

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