PRODUCT MONOGRAPH

pms-NAPROXEN

(Naproxen Tablets, U.S.P.)
(Naproxen Suppositories, B.P.)

125, 250, 375 and 500 mg TABLETS

500 mg SUPPOSITORIES

ANTI-INFLAMMATORY AGENT WITH ANALGESIC & ANTIPYRETIC PROPERTIES

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory agent with analgesic and antipyretic properties.

ACTION AND CLINICAL PHARMACOLOGY

Naproxen has demonstrated anti-inflammatory, analgesic and antipyretic properties in classical animal test systems. In patients with rheumatoid arthritis, the anti-inflammatory action has been shown by a reduction in joint swelling, pain, and duration of morning stiffness, and by enhanced grip strength and increased mobility.

It exhibits an anti-inflammatory effect even in adrenalectomized animals and therefore its action is not mediated through the pituitary-adrenal axis. It is not a corticosteroid.

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

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

Naproxen absorbs virtually completely from the upper gastro-intestinal tract. The rate of absorption is relatively slow. The time to reach peak plasma concentration following rectal administration of Naproxen 500 mg suppository is similar to that for the oral tablet, occurring 2 to 3 hours after dosing.

The mean biological half-life for Naproxen suppository ranges from 16.8 to 17.5 hours. The AUC 0 --> ∞ is similar to that of Naproxen tablet.

At therapeutic levels, Naproxen is 99% protein bound. Elimination occurs via the urine, 70% of the dose is eliminated as free Naproxen and its glucuronic acid conjugate. About 28% of the dose is metabolized and is eliminated as 6-0-desmethyl Naproxen and its conjugate.

BIOAVAILABILITY

A bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single oral 500 mg dose of Naprosyn 250 mg and pms-NAPROXEN 250 mg tablets was measured and compared. The results can be summarized as follows:

PARAMETER	MEANS		% Diffr
	NAPROSYN	pms-NAPROXEN	
AUC 0-32 hrs. (mcg-h/mL)	931.0	912.6	-2.0
C_{max} (mcg/mL)	73.4	73.8	+0.5
T_{max} (hrs.)	2.1	2.1	0
$T_{½}$ (hrs.)	14.3	14.2	-0.7

A bioavailability-study was also performed comparing the rate and extent of absorption of a single rectal dose of Naprosyn 500 mg vs. pms-NAPROXEN 500 mg suppositories. The results can be summarized as follows:

PARAMETER	GEOMETRIC MEAN ARITHMETIC MEAN (C.V.)				RATIO
	REFERENCE		TEST		
AUC_T (µg·hr/mL)	999.92 1017.34	(17.69)	983.84 998.81	(16.86)	98.39%
AUC_∞ (µg·hr/mL)	1170.74 1196.05	(20.50)	1162.30 1182.28	(18.15)	99.28%
C_{max} (µg/mL)	53,34 54.32	(18.61)	56.44 57.28	(17.15)	105.81%
* T_{max} (hours)	2.52	(1.07)	2.44	(0.5)	---
$T_{½el}$ (hours)	16.77	(4.47)	17.21	{5.73)	---

* For the T_{max} and $T_{½}$ el parameters these are the arithmetic means (standard deviation).

The values for the T_{max} and $T_{½}$ for pms-NAPROXEN 500 mg suppositories are similar to those reported in other studies.

INDICATIONS AND CLINICAL USES

pms-NAPROXEN (Naproxen) is indicated for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

CONTRAINDICATIONS

pms-NAPROXEN (Naproxen) is contraindicated in patients with active peptic ulcers or active inflammatory diseases of the gastrointestinal tract.

pms-NAPROXEN is also contraindicated in patients with known or suspected hypersensitivity to it or to Naproxen sodium.

pms-NAPROXEN should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other non-steroidal anti-inflammatory agents. Fatal anaphylactoid reactions-have occurred.

pms-NAPROXEN suppositories are contraindicated in children under 16 years of age. The suppositories are also contraindicated in patients with any inflammatory lesions of rectum or anus 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 non-steroidal anti-inflammatory drugs (NSAID's) including Naproxen.

pms-NAPROXEN (Naproxen) should be given under close medical supervision to patients prone to gastro-intestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastro-intestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including pms-NAPROXEN should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastro-intestinal 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 non-steroidal 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 end 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. Because of the known effect of drug of this class on the human fetal cardiovascular system (closure of ductus arteriosus) use during late pregnancy should be avoided.

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

Specific precautions

pms-NAPROXEN (Naproxen) should not be used concomitantly with any drug containing Naproxen sodium, since both circulate in plasma as the Naproxen anion.

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 with non-steroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

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.

General Precautions

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. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients.

Gastrointestinal system:

If peptic ulceration is suspected or confirmed, or if gastro-intestinal bleeding or perforation occurs pms-NAPROXEN 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 gastro-intestinal side effects or allow continuation of pms-NAPROXEN therapy when and if these adverse reactions appear.

Renal function:

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 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, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of Naproxen should be anticipated in patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Caution should be used if the drug is given to patients with creatinine clearance of less than 20 mL/minute because accumulation of Naproxen metabolites has been seen in such patients.

Hepatic 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. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. 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 the 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. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients.

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with Naproxen, Therefore, as with many other non-steroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. pms-NAPROXEN should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

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

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 pms-NAPROXEN 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 g or less who are to receive long term therapy should have hemoglobin values determined frequently.

Infection:

In common with other anti-inflammatory drugs, pms-NAPROXEN (Naproxen) may mask the usual signs of infection.

Ophthalmology:

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

Drug Interactions:

Naproxen may displace from their binding sites other drugs which are also albumin-bound and may lead to drug interactions. For example, in a patient receiving bishydroxycoumarin or warfarin, the addition of pms-NAPROXEN to therapy could prolong the prothrombin time. Patients, receiving both drugs should be under careful observation. Similarly, patients receiving pms-NAPROXEN and a hydantoin, sulfonamide, or sulfonylurea should be observed for signs of toxicity.

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 anti-hypertensive effect of propranolol and other beta-blockers.

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 should be used if this drug is administered concomitantly with methotrexate. Naproxen and other non-steroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly enhancing the toxicity of that drug.

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 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-hydroxycorticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that Naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed.

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

ADVERSE REACTIONS

The most common adverse reactions encountered with non-steroidal 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.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below.

** Denotes incidence of reported reactions between 3% and 9%.

* Denotes incidence of reported reactions between 1% and 3%.

Reactions occurring in less than 1% of the patients are unmarked.

Gastrointestinal:

Heartburn**, constipation**, abdominal pain**, nausea**, diarrhea*, dyspepsia*, stomatitis*, diverticulitis*, gastrointestinal bleeding, hematemesis, melena, peptic ulceration with or without bleeding and/or perforation, vomiting.

Dermatologic:

Pruritis**, ecchymoses**, skin eruptions**, sweating*, purpura*, alopecia, urticaria and skin rashes, erythema multiforme, angioneurotic edema, Stevens-Johnson Syndrome, epidermal necrolysis, photosensitivity dermatitis, exfoliative dermatitis, erythema nodosum.

Central Nervous System:

Headache**, dizziness**, drowsiness**, lightheadedness*, vertigo*, depression*, and fatigue*. Only a few patients had to discontinue treatment because of severity of some of these complaints (headache and dizziness). Other adverse effects were inability to concentrate, malaise, myalgia, insomnia, cognitive dysfunction (i.e. decreased attention span, loss of short-term memory, difficulty with calculations).

Hematologic Reactions

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

Cardiovascular Reactions:

Dyspnea**, peripheral edema**, palpitations* congestive heart failure, and vasculitis.

Hepatic:

Jaundice, cholestasis, hepatitis, abnormal liver function tests.

Renal:

Glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, nephropathy and tabular necrosis.

Special Senses:

A few eye abnormalities, including corneal changes, lens opacities, macular degeneration, and blurred vision were reported in patients with Naproxen. Tinnitus **, and hearing disturbances or impairment *.

Others:

Thirst *, muscle weakness, anaphylactoid reactions, menstrual disorders, pyrexia, hyperglycemia, hypoglycemia, hematuria and eosinophilic pneumonitis.

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 3000 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.

Should a patient ingest a large number of tablets, accidently or purposefully, the stomach may be emptied and usual supportive measures employed. Animal studies suggest that the prompt administration of 5 grams of activated charcoal would tend to reduce markedly the absorption of the drug.

DOSAGE AND ADMINISTRATION

Adult:

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

Rectal

pms-NAPROXEN 500 mg suppositories can replace one of the oral doses in patients receiving 1000 mg of pms-NAPROXEN daily. Administration of pms-NAPROXEN more frequently than twice daily is not necessary.

Clinical experience has shown that steroids can often be decreased and sometimes eliminated when Naproxen is administered.

Children:

Due to lack of clinical experience, pms-NAPROXEN suppositories are not recommended for use in children under 16 years of age.

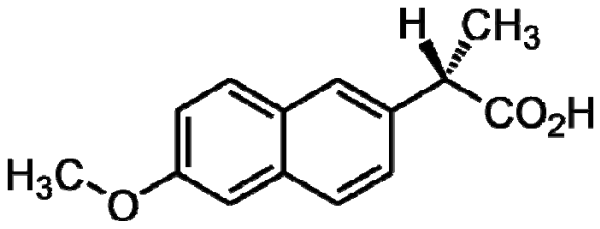
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Naproxen

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

Structural formula:



Molecular Formula: $C_{14}H_{14}0_3$

Molecular Weight: 230.27

Description: Naproxen is an odourless 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.

pKa = 4.15

Composition: pms-NAPROXEN suppositories contain triglycerides as the non-medicinal ingredients.

Stability and Storage Recommendations
Store between 15-30^{0}C.

AVAILABILITY OF DOSAGE FORMS

pms-NAPROXEN 500 mg suppositories: Each white to off-white opaque suppository contains 500 mg of Naproxen. Available in boxes of 10 and 30 molded in polyethylene - lined white PVC molds in perforated strips of 5 suppositories.

pms-NAPROXEN 125 mg Tablets: Each pale green, oval biconvex tablet engraved PMS-125 contains 125 mg Naproxen. Available in bottles of 100, 500 and 1000 tablets.

pms-NAPROXEN 250 mg Tablets: Each yellow, oval, biconvex tablet engraved PMS-250 contains 250 mg Naproxen. Available in bottles of 100, 250, 500 and 1000 tablets.

pms-NAPROXEN 375 mg Tablets: Each peach-coloured, capsule-shaped tablet engraved PMS-375 contains 375 mg Naproxen. Available in bottles of 100 and 500 tablets.

pms-NAPROXEN 500 mg Tablets: Each yellow, capsule-shaped tablet engraved PMS-500 contains 500 mg Naproxen. Available in bottles of 100 and 500 tablets.

PATIENT INFORMATION

pms-NAPROXEN (Naproxen) which has been prescribed to you by your doctor, is one of a large group of non-steroidal anti-inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

You should take pms-NAPROXEN only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

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

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 diarrhea) occurs and continues, contact your doctor.

SCHEDULE OF ADMINISTRATION

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

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

Along with its beneficial effects, pms-NAPROXEN 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 diarrhea;
- yellow discoloration of the skin or eyes, with or without fatigue;
- any changes in the amount of color 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, lightheadedness; hearing problems.

ALWAYS REMEMBER

- Before taking this medication tell your doctor and pharmacists if your

- are allergic to pms-NAPROXEN or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin;
- have a history of stomach upset, ulcers, or liver or kidney diseases; 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 lightheaded after taking this medication;

- 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 checkups are essential.

- if you require more information an this drug, consult your doctor or pharmacist.

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 has 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 or 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 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 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: 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 plasma half-life of approximately 14 hours. The preferred route of excretion is via the urine, with only 1 percent of the dose excreted in the feces. The drug is excreted similarly by both the male and female. Following 14 days of continuous exposure to the drug, there was no indication of induction of metabolizing enzymes.

Naproxen was found to be rapidly absorbed from the gastrointestinal tract. Blood levels achieved in the human following oral administration were only slightly lower than after intravenous injection. Steady-state appears to be obtained within the first days of Naproxen administration.

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.

Effect of Naproxen on acetylsalicylic acid-induced gastrointestinal 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 to 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:

Rats:	520 mg/Kg
Mice:	1230 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. Tabular dilation (ectasia) occurred in rabbits dosed orally for 14 days with 200 mg/Kg/day or more of Naproxen. An examination of unfixed renal tissue from rabbits so treated was conducted and revealed the presence of diffraction patterns similar to that of crystalline Naproxen. This suggests that the ectasia observed was a physical response to deposition of excreted Naproxen within the tubules.

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

A wide variation in susceptibility to gastrointestinal lesions from administration of Naproxen was evident in the various species tested. For example, 30 mg/Kg/day was tolerated well by rats for 90 days, but the same dose was ulcerogenic when administered for 6 months.

Rhesus monkeys and miniature swine exhibited no significant pathology when dosed with Naproxen at 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 one 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 amount 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 doses of Naproxen on the gastrointestinal tract. Moderate weight loss of the male secondary sex glands occurred in some studies in naproxen treated rat and dogs. Histopathologically, the affected glands in some instances exhibited atrophic and/or hypoplastic changes characterized by decreased secretory material. A possible estrogenic action of Naproxen as a causative factor seems highly unlikely since in standard bioassay procedures, the drug exhibited no estrogenic activity. Nevertheless, daily doses of Naproxen as high as 30 mg/Kg administered for 60 days before mating had no effect on fertility and reproductive performance of male rats. These results reflect the physiological integrity of the entire male reproductive apparatus after administration of Naproxen throughout the spermatogenic cycle.

Effect on Induced Infections in Rabbits

To determine whether treatment with Naproxen affects the ability of animals to respond to bacterial infection, rabbits were inoculated subcutaneously with Diplococcus 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 anogenital 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 pugs, 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 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 groups 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 (acetylsalicylic acid, indomethacin, mefenamic acid and phenylbutazone). Similar results have been suggested in reports of other animal studies with mefenamic acid and ibuprofen.

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