PRODUCT MONOGRAPH

NU-NAPRO-Na

NU-NAPRO-Na DS

Naproxen Sodium Tablets USP

275 mg and 550 mg

Analgesic, anti-inflammatory agent

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DATE OF PREPARATION:
October 20, 2009

Control#: 133519

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NAME OF DRUG

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THERAPEUTIC CLASSIFICATION

Analgesic, anti-inflammatory agent

ACTIONS AND CLINICAL PHARMACOLOGY

Naproxen sodium has demonstrated analgesic, anti-inflammatory and antipyretic properties in human clinical studies and in classical animal test systems. 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. It inhibits prostaglandin synthetase, as do certain other nonsteroidal analgesic/anti-inflammatory agents. As with other agents, however, the exact mechanism of its anti-inflammatory and analgesic actions is not known.

Blood loss and gastroscopy studies with normal volunteers showed that daily administration of 1100 mg of naproxen sodium caused significantly less gastric bleeding and erosion than 3250 mg of ASA.

At the recommended dosage, the analgesic effect of naproxen sodium was shown to be comparable to that observed using 650 mg of ASA. The analgesic effect is obtained within one hour and can last at least 7 hours.

Pharmacokinetics

Naproxen sodium is freely soluble in water and is completely absorbed from the gastrointestinal tract. Plasma levels are obtained in patients within 20 minutes and peak levels in 1 hour. It is extensively bound to plasma protein and has a plasma half-life of approximately 13 hours. The preferred route of excretion is via the urine with only 1 % of the dose excreted in the feces.

A bioavailability study was performed using normal human volunteers. The rate and extent of absorption of naproxen after a single oral 550 mg dose of Anaprox 275 mg and

Nu-Napro-Na 275 mg tablets was measured and compared. The results are summarized as follows:

Parameter	Anaprox 275 mg	Nu-Napro-Na 275 mg	% Diffr.
AUC 0-32 (mcg*hrs/mL)	857.3	834.9	-2.6
C_{max} (mcg/mL)	83.0	81.2	-2.2
T_{max} (hrs)	1.3	0.9	-32.9
$t_{½}$ (hrs)	14.0	14.2	+1.4

INDICATIONS AND CLINICAL USE

NU-NAPRO-Na or NU-NAPRO-Na DS (napoxen sodium) is indicated for the relief of mild to moderately severe pain accompanied by inflammation in conditions such as musculo-skeletal trauma and post-dental extraction. It is also indicated for the relief of pain associated with post-partum cramping and dysmenorrhea.

CONTRAINDICATIONS

Napoxen sodium is contraindicated in patients with peptic ulcer or active inflammatory diseases of the gastrointestinal system.

Known or suspected hypersensitivity to the drug

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 anaphylactoid 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 (NSAIDs) including naproxen sodium.

Am-NAPRO-Na and NU-NAPRO-Na 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 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 (NSAIDs). 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 Pregnant and Lactating Women

The safety of this drug in pregnancy and lactation has not been established and its use during these events is therefore not recommended. 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. Similar results have been found with other nonsteroidal 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.

The naproxen anion readily crosses the placental barrier. It has been found in the milk of lactating women at a concentration approximately 1 % of that found in the plasma.

PRECAUTIONS

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

Use in the Elderlv Patient:

One study indicates that after the administration of naproxen, 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 sodium 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.

Gastrointestinal System:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs NU-NAPRO-Na or NU-NAPRO-Na DS should be discontinued, an appropriate treatment instituted and the patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of naproxen sodium therapy when and if these adverse reactions appear.

NU-NAPRO-Na and NU-NAPRO-Na DS should be given under close supervision to patients prone to gastrointestinal tract irritation, in patients with a history of peptic ulcer, or in patients with diverticulosis. Gastrointestinal bleeding sometimes severe and occasionally fatal, and peptic ulcer have occurred in patients receiving naproxen.

Renal Function:

As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen sodium 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 nonsteroidal 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. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.
Naproxen sodium 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. In these cases lower doses of naproxen sodium should be anticipated and patients carefully monitored.

During long-term therapy, kidney function should be monitored periodically. In clinical trials a few patients developed mild elevations in BUN. The significance of this is unknown.

Naproxen sodium should not be used chronically in patients having baseline creatinine less than 20 mL/minute.

Hepatic Function:

As with other nonsteroidal 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 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, of 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 sodium dosing is unknown, but caution is advised when high doses are required. It is prudent to use the lowest effective dose.

Fluid and Electrolyte Balance:

Fluid retention and edema 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. NU-NAPRO-Na and NU-NAPRO-Na DS 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.

Each NU-NAPRO-Na tablet contains approximately 25 mg of sodium and each NU-NAPRO-Na DS tablet contains approximately 50 mg of sodium. 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, the drug should be used with caution in patients with fluid retention, hypertension or heart failure.

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 naproxen sodium is administered.

Blood dyscrasias associated with the use of nonsteroidal anti-inflammatory drugs are rare, but could be associated 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 naproxen sodium may mask the usual signs of infection and the physician should be alert for development of infection in patients receiving NU-NAPRO-Na or NU-NAPRO-Na DS.

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.

Central Nervous System:

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

Hypersensitivity Reactions:

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

Cardiovascular Function:

It is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking naproxen sodium.

Use in Children:

NU-NAPRO-Na and NU-NAPRO-Na DS are not recommended in children under 16 years of age because the safety and dose schedule have not been established in this age group.

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 naproxen sodium could prolong the prothrombin time. These patients should, therefore, be under careful observation. Similarly, patients receiving naproxen sodium 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. lnhibition of renal lithium clearance leading to increases in plasma lithium concentrations have also been reported.

Naproxen sodium and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta blockers.

The rate of absorption of naproxen sodium 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 sodium and methotrexate since naproxen and other nonsteroidal anti-inflammatory agents have been reported to reduce the tubular secretion of methotrexate in an animal model, thereby possibly enhancing its toxicity.
Laboratory Tests:

NU-NAPRO-Na and NU-NAPRO-Na DS decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined. 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-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 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.

Adverse reactions reported in controlled clinical trials 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 during controlled clinical trials and through voluntary reports since marketing are unmarked.

Gastrointestinal:

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

Central Nervous Svstem:

Headache (1) , dizziness (1) , drowsiness (1) , lightheadedness (2), vertigo (2), depression (2) and fatigue (2). Occasionally patients had to discontinue treatment because of the severity of some of these complaints (headache and dizziness). Other adverse effects were inability to concentrate, malaise, myalgia, insomnia and cognitive dysfunction (i.e. decreased attention span, loss of short-term memory, difficulty with calculations).

Dermatologic:

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

Cardiovascular Reactions:

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

Special Senses:

Tinnitus (1), hearing disturbances (2), hearing impairment and visual disturbances.

Hematologic:

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

Renal:

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

Hepatic Changes:

Abnormal liver function tests, jaundice, cholestasis and hepatitis.

Others:

Thirst (2)**,** muscle weakness, anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever), angioneurotic edema, hyperglycemia, hypoglycemia, hematuria, hepatitis 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 3,000 mg of naproxen. One patient ingested a single dose of 25 g 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, 411 0 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of naproxen sodium tablets, 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. In dogs, 0.5 g/kg of charcoal was effective in reducing the plasma levels of naproxen when given after the drug. 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

The recommended starting dose of NU-NAPRO-Na (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 NU-NAPRO-Na DS tablet (550 mg naproxen sodium) given twice daily may be used.

The following text will be dispensed with this drug:

PATIENT INFORMATION LEAFLET

NU-NAPRO-Na

NU-NAPRO-Na DS

Brand of Naproxen Sodium Tablets

Read the underlined information first. Then go back and read the rest. If you do not recognize the names of medical conditions or medicines included in this information check with your doctor or pharmacist.

Naproxen sodium (na-PROX-en SOE-dee-um) which has been prescribed to you by your doctor, is one of a large group of nonsteroidal anti-inflammatory drugs (NSAIDs) and is used to relieve some symptoms caused by arthritis, such as inflammation, swelling, stiffness, joint pain and fever by reducing the production of certain substances (prostaglandins). Naproxen sodium is also used to relieve mild to moderately severe pain accompanied by inflammation (sprains, strains, bursitis, tendinitis, post-dental extraction). It is also used to relieve other kinds of pain (post-labour cramps, menstrual pains).

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 you are otherwise directed by your doctor.

- In order for this medicine to work, it must be taken as directed.

- Keep all medicines out of the reach of children.

- If you want more information about this medicine, ask your doctor, nurse, or pharmacist.

- If any of the following information causes you special concern, do not decide against taking this medicine without first checking with your doctor.

- Your regular medical checkups are essential.

Before Using This Medicine

In order to decide on the best treatment for your medical problem, your doctor should be told:

- if you have ever had any unusual or allergic reaction, such as skin rash, hives, or itching or breathing problems (wheezing or asthma), to naproxen sodium or to any arthritis or nonsteroidal anti-inflammatory medication, such as:

  Acetylsalicylic acid (ASA) or other salicylates
  Diclofenac
  Diflunisal
  Fenoprofen
  Flurbiprofen
  lbuprofen
  lndomethacin
  Ketoprofen
  Mefenamic acid
  Oxyphenbutazone
  Phenylbutazone
  Piroxicam
  Sulindac
  Tiaprofenic acid
  Tolmetin

- if you are pregnant or if you intend to become pregnant while taking this medicine. Studies on birth defects with naproxen sodium have not been done in humans. However, if taken late in pregnancy, there is a chance that naproxen sodium may cause unwanted effects on the heart or blood flow in the fetus or newborn infant. Also, studies in animals have shown that naproxen sodium, if taken late in pregnancy, may increase the length of pregnancy, prolong labor, or cause other problems during delivery.

- if you are breast-feeding an infant. Naproxen sodium passes into the breast milk and should be avoided in nursing mothers.

- if you have any of the following medical problems:

  Asthma
  Bleeding problems
  Colitis, stomach ulcer, or other stomach problems
  Heart disease .
  High blood pressure
  Kidney disease
  Liver disease

- if you are now taking any of the following medicines or types of medicine:

  Acetaminophen
  Anticoagulants (blood thinners)
  Acetylsalicylic acid or other salicylates

Heparin
lnflammation medicine (for example, acetylsalicylic acid or other arthritis medicine)
Probenecid

- If you have any other medical problems.

Proper Use of This Medicine

In order for this medicine to help you, it must be taken regularly as ordered by your doctor. During treatment your doctor may decide to adjust the dosage according to your response to the medication.

You should take this medicine with food or milk to lessen stomach upset. If stomach upset (indigestion, nausea, vomiting, stomach pain, or diarrhea) occurs and continues or if you have any question about how you should be taking this medicine, check with your doctor.

If you miss a dose of this medicine, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.

Do not double doses.

How to store this medicine:

- Store away from heat and direct light, out of the reach of children.
- Do not store in the bathroom medicine cabinet because the heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed. Flush it down the toilet.

Precautions While Using This Medicine

Your doctor should check your progress at regular visits in order to make sure that this medicine provides relief and does not cause unwanted effects.

Do not take ASA (acetyl salicylic acid) or ASA-containing compounds or other drugs used to relieve symptoms of arthritis or drink alcoholic beverages while taking this medicine, unless otherwise directed by your doctor.

Too much use of acetaminophen together with naproxen sodium may increase the chance of kidney problems. Therefore, do not regularly take acetaminophen together with naproxen sodium, unless your doctor has directed you to do so.

Before having any kind of surgery (including dental surgery), tell the physician or dentist in charge that you are taking this medicine.

This medicine may cause some people to become dizzy, lightheaded, or less alert than they are normally. Make sure you know how you react to this medicine before you drive, use machinery, or do other jobs that require you to be alert.

For patients on a sodium-restricted (low-salt) diet - this medicine contains 25 mg of sodium in each NU-NAPRO-Na tablet and 50 mg of sodium in each NU-NAPRO-Na DS tablet. If you have a question about this check with your doctor or pharmacist.

Side Effects of This Medicine

Along with its beneficial effects, naproxen sodium, like other NSAIDs, 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 appear very often, when they do occur they may require medical attention. Check with Your doctor immediately if any of the following side effects occur:

More common

Shortness of breath, troubled breathing, wheezing, or tightness in chest, indigestion, nausea, vomiting, stomach pain.

Rare

Sore throat and fever
Unusual bleeding or bruising
Yellowing of eyes or skin
Bloody or cloudy urine
Sudden decrease in amount of urine
Bloody or black tarry stools; skin rash, swelling, hives or itching; diarrhea; swelling of feet or lower legs; blurred vision or any visual disturbances; any change in the colour of urine.

Also, check with your doctor as soon as possible if any of the following side effects occur:

More common

Itching of skin
Ringing or buzzing in ears
Unusual weight gain

Less common

Decreased hearing or any loss of hearing

Rare

Muscle weakness
Mental depression
Chills and fever
Difficult or painful urination
Frequent urge to urinate
Unusual tiredness or weakness
Hives or skin rash

Other side effects may occur which usually do not require medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

More common

Heartburn or indigestion
Nausea or vomiting
Stomach pain or discomfort
Constipation
Dizziness or lightheadedness
Headache
Drowsiness

Less common or rare

Diarrhea
Irritation or soreness of mouth
Unusual pounding heartbeat
Unusual sweating
Other side effects not listed above may also occur in some patients.

If you notice any other effects, check with your doctor.

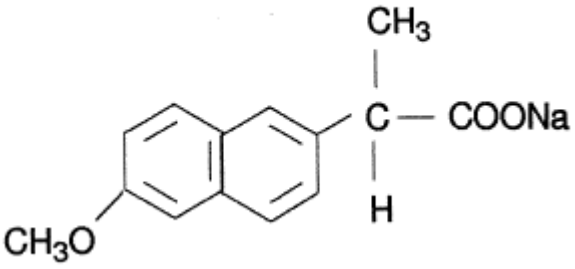
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: naproxen sodium

Chemical Name: (-)sodium 2-(6-methoxy-2-naphthyl) propionate

Structural Formula:



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

Molecular Weight: 252.25

Description: Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water with a melting point of about 255°C with decomposition.

Composition

In addition to naproxen sodium, each NU-NAPRO-Na tablet and each NU-NAPRO-Na DS tablet contains the non-medicinal ingredients microcrystalline cellulose, dextrates, magnesium stearate, stearic acid, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and FD&C Blue #2.

Stability and Storage Recommendations

Store at controlled room temperature, 15-30° C.

AVAILABILITY OF DOSAGE FORMS

NU-NAPRO-Na 275 mg tablets

- each blue, oval, film-coated tablet, engraved " 275" on one side and plain on the other, contains 275 mg of naproxen sodium.

- available in bottles of 100 and 500 tablets.

NU-NAPRO-Na DS 550 mg tablets

- each blue, oval, film-coated tablet, engraved "550" on one side and plain on the other, contains 550 mg of naproxen sodium.

- available in bottles of 100 and 500 tablets.

PHARMACOLOGY

A variety of pharmacologic tests were employed in assessing the analgesic, antipyretic and anti-inflammatory activities of naproxen sodium. It has been convincingly shown in man and animals that regardless of which drug (naproxen or naproxen sodium) is administered, the circulating moiety in the plasma 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. There were no discrepancies or exceptions evident.

Analgesic Activity

Depending on the assay used, naproxen sodium had less analgesic activity than indomethacin; it was more active than ASA, phenylbutazone and mefenamic acid. Like ASA, phenylbutazone and other "anti-inflammatory analgesics", naproxen sodium raised the pain threshold only in experimental pain states involving inflammation (unlike morphine, which raises the pain threshold in both inflamed and uninflamed states). Further support for this contention is the fact that naproxen sodium did not raise heat-induced pain threshold responses as shown in the "Hot Plate Test".

Antipyretic Activity

As an antipyretic in the rat, using yeast-induced fever, naproxen sodium was about as active as indomethacin, but more active than phenylbutazone and ASA.

Anti-inflammatory Activity

Depending on the test system used, naproxen and naproxen sodium are slightly less active than indomethacin, and more active than hydrocortisone, ASA, phenylbutazone and mefenamic acid. Based on anti-edema effects in the rat, the duration of anti-inflammatory action of naproxen appears to be relatively short; however, these findings may only be relevant to this species, since metabolic half-life determinations in man indicate a much longer duration of action.

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

As measured by the cotton-pellet-test, naproxen sodium produced significant inhibition of granuloma tissue over a relatively wide dose range (5-30 mg/kg/day), without affecting body weight or inducing other toxic manifestations.

Prostaglandin Synthesis Inhibition

Naproxen sodium inhibits the synthesis of prostaglandins E_2 and $F_{2\alpha}$ from arachidonic acid by bovine seminal vesicle microsomes and by pregnant rat uterine microsomes. It also suppresses PGE_2 production in cultures of rheumatoid synovial tissue and inhibits arachidonate-induced fetal bone resorption in vitro. The delay of parturition seen with naproxen sodium and other nonsteroidal anti-inflammatory agents might be explained by this ability to inhibit uterine prostaglandin biosynthesis since prostaglandins are known to stimulate uterine smooth muscle contractions both in vitro and in vivo. It has been recognized for some time that they play an important role in initiating labour at term.

Naproxen sodium inhibited the biosynthesis of both PGF_2 and $PGE_{2\alpha}$, by pregnant rat uterine microsomes in a dose dependant 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.

Naproxen sodium also greatly decreased $PGF_{2\alpha}$, levels in the uteri of pregnant rats receiving oral doses of the drug for three days during late stages of pregnancy, confirming the in vitro effects seen with naproxen sodium in inhibiting PG synthetase.

Cardiovascular and Central Nervous Svstem Effects

Acute studies were carried out to determine the effects of naproxen sodium on the cardiovascular and central nervous systems. Naproxen sodium was almost inert in cardiovascular system studies. Its CNS effects were minimal.

It was also determined that the effects of excessive amounts of naproxen sodium can be controlled by CNS depressants such as phenobarbital, pentobarbital, or chlordiazepoxide.

Effects on Reproductive System

Several studies were carried out to determine the drugs' effects on the reproductive system. Naproxen did not demonstrate estrogenic, anti-estrogenic or androgenic effects. High, toxic dose levels decreased pregnancies; this appeared to be an indirect consequence of general toxicity rather than a true antifertility effect.

Pharmacology of Major Metabolite

The major metabolite of naproxen, 6-desmethyl naproxen was tested in a variety of pharmacologic preparations measuring diverse activities. From these studies it was concluded that the metabolite was only very weakly active in all pharmacoiogic assays in laboratory animals.

Animal Metabolism

The metabolism of naproxen has been studied in a variety of animal species including the rat, beagle dog, guinea pig, rhesus monkey, minipig and man.

Naproxen was found to be rapidly absorbed from the GI tract of all animals tested, with the dog being the most efficient and the rat the least. The plasma half-life of naproxen ranged from 2 hours in the rhesus monkey to 35 hours in the dog, with the value in the human being approximately 14 hours. The species nearest the human in this regard was the guinea pig with a half-life of 9 hours. The distribution of radioactivity in the various tissues and organs of the rat showed that no unusual amount was retained in the animal 24 hours after administration, nor did there seem to be any selective uptake in any of the tissues analyzed.

CLINICAL PHARMACOLOGY

Since naproxen is a weak acid with a pKa = 5 and because most of the body fluids have a pH higher than 5 (except the contents of the stomach) 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 into the central circulatory system the distributive, metabolic and excretory fate 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 plasma half-life of approximately 13 hours. The preferred route of excretion is via the urine with only 1% of the dose excreted in the feces. 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 metabolizing 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, about 10% of the body weight in man. This index 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 (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. 70 % of the ingested dose was eliminated either as unchanged naproxen (10%) or as conjugated naproxen (60%). This conjugated fraction was comprised of 40 % naproxen glucuronide and 20 % other conjugates including glycine and sulfate 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 demethylated 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 fell short of the linear projections. 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.

TOXICOLOGY

Naproxen sodium is the sodium salt of naproxen. In a variety of animal species and in man, the circulating plasma entity is the same (napoxen 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 LD50 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 in rats, mice, rabbits and monkeys dosed with naproxen. 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. 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.

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.

In rhesus monkeys given oral doses of 100 mg/kg/day or more of naproxen for 12 months, dose-related renal lesions were observed. The changes included multi-focal chronic active

nephritis, which involved all components of the kidney in the most severely affected animals, and papillary tip necrosis.

A wide range of 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 180 mg/kg/day (90 mg/kg b.i.d.) for 12 months produced only mild irritation of the gastric mucosa. In rabbits the maximum tolerated repeated oral dose is 80 to 100 mg/kg/day. Mice survived oral daily doses of 240 mg/kg/day for 6 months. In dogs, on the other hand, 5.0 mg/kg/day approaches the maximum tolerated dose.

This peculiar canine susceptibility to gastrointestinal effects of nonsteroidal 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 in 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, monkey, and man, 86-90% of the administered drug is excreted in the urine. The suggested enterohepatic circulation of naproxen in the dog (as judged by fecal excretion) most likely is 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 (see PHARMACOLOGY).

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.

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 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 fetuses, resorption, fetal 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 number of live fetuses in both dose groups and in fetal body weight in the high dose group.

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 number 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.

Recent evidence, however, suggests that inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory compounds may be related to decreased uterine contractibility. Thus, the onset of labour 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 nonsteroidal 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 reproduction study in mice, the dams were dosed daily with 12, 36 or 108 mg/kg from 14 days prior to mating through weaning. At the highest dose level, there was an increase in maternal deaths which was reflected in decreased 21 day survival and lactation indices. There were no other changes in the parameters examined. In a similar study in rats, daily doses were 2, 10 or 20 mg/kg from 14 days before mating through weaning. Other than decreased survival to weaning which appeared due to poor maternal care in pups born to high dose dams, there were no differences between control and treated groups. 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 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.

CARCINOGENICITY AND MUTAGENICITY

A two-year study was performed in rats to evaluate the carcinogenic potential of the drug. No evidence of carcinogenicity was found.

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

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