PDR®

53

EDITION

1999

PHYSICIANS' DESK REFERENCE®

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NDC 0008-0235-50, 2 mL size Blunt Pointe™

NDC 0008-0235-01, 2 mL size (22 gauge x 1-1/4 inch needle).

Mepergan (meperidine HCl and promethazine HCl) Injection is also available in vials as follows:

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Use carton to protect contents from light

Store at room temperature, approximately 25° C (77° F)

Manufactured by:

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Philadelphia, PA 19101

NAPRELAN® Rx

[nă' prĕ-lăn]

(naproxen sodium)

CONTROLLED RELEASE TABLETS

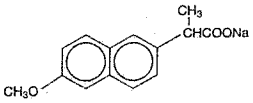
Equivalent to 375 mg and 500 mg naproxen

DESCRIPTION

Naprelan contains naproxen sodium, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs).

Naprelan uses the proprietary IPDAS™ (Intestinal Protective Drug Absorption System) technology. It is a rapidly disintegrating tablet system combining an immediate release component and a sustained release component of microparticles that are widely dispersed, allowing absorption of the active ingredient throughout the gastrointestinal (GI) tract, maintaining blood levels over 24 hours.

The chemical name for naproxen sodium is 2-naphthaleneacetic acid, 6-methoxy-α-methyl-sodium salt, (S)- with the following structural formula:



Naproxen sodium

Molecular Formula: $C_{14}H_{13}NaO_3$ Molecular Weight: 252.24

Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water.

Naprelan contains 412.5 mg or 550 mg of naproxen sodium, equivalent to 375 mg and 500 mg of naproxen and 37.5 mg and 50 mg sodium respectively. Each Naprelan tablet also contains the following inactive ingredients: ammonio methacrylate copolymer Type A, ammonio methacrylate copolymer Type B, citric acid, crospovidone, magnesium stearate, methacrylic acid copolymer Type A, microcrystalline cellulose, povidone, and talc. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

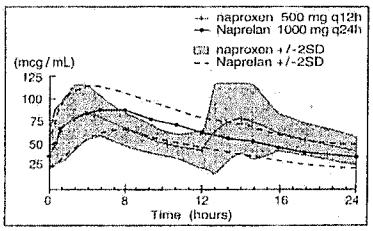
CLINICAL PHARMACOLOGY

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. As with other NSAIDs, its mode of action is not fully understood; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

PHARMACOKINETICS

Although naproxen itself is well absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels for a given dose. Approximately 30% of the total naproxen sodium dose in Naprelan is present in the dosage form as an immediate release component. The remaining naproxen sodium is coated as microparticles to provide sustained release properties. After oral administration, plasma levels of naproxen are detected within 30 minutes of dosing, with peak plasma levels occurring approximately 5 hours after dosing. The observed terminal elimination half-life of naproxen from both immediate release naproxen sodium and Naprelan is approximately 15 hours. Steady state levels of naproxen are achieved in 3 days and the degree of accumulation in the blood is consistent with this

Plasma Naproxen Concentrations Mean of 24 Subjects (+/-2SD) (Steady State, Day 5)



Pharmacokinetic Parameters at Steady State Day 5 (Mean of 24 Subjects)

Parameter (units)	naproxen 500 mg Q12h/5 days (1000 mg)			Naprelan 2 x 500 mg tablets (1000 mg) Q24h/5 days		
	Mean	SD	Range	Mean	SD	Range
AUC 0-24 (mcgxh/mL)	1446	168	1167–1858	1448	145	1173–1774
C_{max} (mcg/mL)	95	13	71–117	94	13	74–127
C_{avg} (mcg/mL)	60	7	49–77	60	6	49–74
C_{min} (mcg/mL)	36	9	13–51	33	7	23–48
T_{max} (hrs)	3	1	1–4	5	2	2–10

Absorption

Naproxen itself is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 95%. Based on the pharmacokinetic profile, the absorption phase of Naprelan occurs in the first 4–6 hours after administration. This coincides with disintegration of the tablet in the stomach, the transit of the sustained release microparticles through the small intestine and into the proximal large intestine. An *in vivo* imaging study has been performed in healthy volunteers which confirms rapid disintegration of the tablet matrix and dispersion of the microparticles.

The absorption rate from the sustained release particulate component of Naprelan is slower than that for conventional naproxen sodium tablets. It is this prolongation of drug absorption processes which maintains plasma levels and allows for once daily dosing.

Food Effects

No significant food effects were observed when twenty-four subjects were given a single dose of Naprelan 500 mg either after an overnight fast or 30 minutes after a meal. In common with conventional naproxen and naproxen sodium formulations, food causes a slight decrease in the rate of naproxen absorption following Naprelan administration.

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is a less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses. However the concentration of unbound naproxen continues to increase proportionally to dose. Naprelan exhibits similar dose proportional characteristics.

Metabolism

Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

Elimination

The elimination half-life of Naprelan and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2–3 doses of Naprelan. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66–92%). A small amount (<5%) of the drug is excreted in the feces. The rate of excretion has been found to coincide closely with the rate of clearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations

Pediatric Use

No pediatric studies have been performed with Naprelan, thus safety of Naprelan in pediatric populations has not been established.

Renal Insufficiency

Naproxen pharmacokinetics have not been determined in tabolized and conjugates are primarily excreted by the kidneys, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

CLINICAL STUDIES

RHEUMATOID ARTHRITIS

The use of Naprelan for the management of the signs and symptoms of rheumatoid arthritis was assessed in a 12 week double-blind, randomized, placebo and active-controlled study in 348 patients. Two Naprelan 500 mg tablets (1000 mg) once daily and naproxen 500 mg tablets twice daily (1000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study.

OSTEOARTHRITIS

The use of Naprelan for the management of the signs and symptoms of osteoarthritis of the knee was assessed in a 12 week double-blind, placebo and active-controlled study in 347 patients. Two Naprelan 500 mg tablets (1000 mg) once daily and naproxen 500 mg tablets twice daily (1000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study.

ANALGESIA

The onset of the analgesic effect of Naprelan was seen within 30 minutes in a pharmacokinetic/pharmacodynamic study of patients with pain following oral surgery. In controlled clinical trials, naproxen has been used in combination with gold, D-penicillamine, methotrexate and corticosteroids. Its use in combination with salicylate is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs the combination may result in higher frequency of adverse events than demonstrated for either product alone.

SPECIAL STUDIES

In a double-blind randomized, parallel group study, 19 subjects received either two Naprelan 500 mg tablets (1000 mg) once daily or naproxen 500 mg tablets (1000 mg) twice daily for 7 days. Mucosal biopsy scores and endoscope scores were lower in the subjects who received Naprelan. In another double-blind, randomized, crossover study, 23 subjects received two Naprelan 500 mg tablets (1000 mg) once daily, naproxen 500 mg tablets (1000 mg) twice daily and aspirin 650 mg four times daily (2600 mg) for 7 days each. There were significantly fewer duodenal erosions seen with Naprelan than with either naproxen or aspirin. There were significantly fewer gastric erosions with both Naprelan and naproxen than with aspirin.

The clinical significance of these findings is unknown.

INDIVIDUALIZATION OF DOSAGE

RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, AND ANKYLOSING SPONDYLITIS

Naprelan like other NSAIDs shows considerable variation in response. The recommended starting dose of Naprelan in adults is two Naprelan 375 mg tablets (750 mg) once daily, or two Naprelan 500 mg tablets (1000 mg) once daily. Patients already taking naproxen 250 mg, 375 mg or 500 mg twice daily (morning and evening) may have their total daily dose replaced with Naprelan as a single daily dose.

During long-term administration, the dose of Naprelan may be adjusted up or down depending on the clinical response of the patient.

In patients who tolerate lower doses of Naprelan well, the dose may be increased to three Naprelan 500 mg tablets (1500 mg) once daily for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating patients, especially at the higher dose levels, the physician should observe sufficient increased clinical benefit to offset the potential increased risk. (See **CLINICAL PHARMACOLOGY**). The lowest effective dose should be sought and used in every patient.

Symptomatic improvement in arthritis usually begins within one week; however, treatment for two weeks may be required to achieve a therapeutic benefit. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see **PRECAUTIONS**). Studies indicate 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. As with other drugs used in the elderly it is prudent to use the lowest effective dose.

ANALGESIA, DYSMENORRHEA, BURSITIS, AND TENDINITIS

The recommended starting dose is two Naprelan 500 mg tablets (1000 mg) once daily. For patients requiring greater analgesic benefit, three Naprelan 500 mg tablets (1500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two Naprelan 500 mg tablets (1000 mg).

Naprelan—Cont.

ACUTE GOUT
The recommended dose on the first day is two or three Naprelan 500 mg tablets (1000–1500 mg) once daily, followed by two Naprelan 500 mg tablets (1000 mg) once daily, until the attack has subsided.

INDICATIONS AND USAGE

Naprelan is indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, and acute gout. It is also indicated in the relief of mild to moderate pain and the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

All naproxen products are contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen. Anaphylactoid reactions may occur in patients without previous known exposure or hypersensitivity to aspirin, naproxen, or other NSAIDs, or in individuals with a history of angioedema, urticaria, bronchospastic reactivity (e.g., asthma), and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment with Naprelan should be discontinued.

WARNINGS

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID THERAPY
Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulcerations and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials with naproxen of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.
Studies to date with all naproxen products have not identified any subset of patients not at risk of developing peptic ulceration and bleeding or any differences between different naproxen products in their propensity to cause peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

GENERAL
NAPRELAN SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN PRODUCTS SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.
The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs.
Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.
Renal Effects
As with other NSAIDs, 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, hematuria, proteinuria, and occasionally nephrotic syndrome associated with naproxen-containing products and other NSAIDs since they have been marketed.
A second form of renal toxicity has been seen in patients taking naproxen as well as other NSAIDs. In patients with prerenal conditions with reduction in renal blood flow or blood volume, renal prostaglandins have a supportive role in the maintenance of renal perfusion. Administration of a NSAID may cause a dose-dependent reduction in prosta- those with impaired renal function, heart failure, liver dysfunction, diuretic use, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.
Naproxen 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. Caution should be used if the drug is given to patients with creatinine clearance of less than 20 mL/minute because accumulation of naproxen has been seen in such patients.
Hepatic Effects
As with other NSAIDs, 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 resolve with continued therapy. The ALT (SGPT) is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) 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 naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with naproxen as with other NSAIDs. 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, fever, etc.), naproxen should be discontinued. Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) 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. It is prudent to use the lowest effective dose.
Fluid Retention and Edema
Peripheral edema has been observed in some patients receiving naproxen. Naprelan (naproxen sodium) tablets contain 37.5 mg or 50 mg of sodium (1.5 mEq or 2.0 mEq respectively). This should be considered in patients whose overall intake of sodium must be severely restricted. For these reasons, Naprelan should be used with caution in patients with fluid retention, hypertension or heart failure.
INFORMATION FOR PATIENTS
Naprelan, like other drugs of its class, is not free of side effects. This formulation of naproxen can cause discomfort and, rarely, there are more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. NSAIDs are often essential agents in the management of arthritis and have a major role in the treatment of pain but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS**) and likely benefits of Naprelan treatment. Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.
LABORATORY TESTS
Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with Naprelan for the signs and symptoms of ulceration and bleeding, and should inform them of the importance of this follow-up and what they should do if certain signs and symptoms do appear. Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically. (See **WARNINGS**—RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID THERAPY).
DRUG INTERACTIONS
The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (See **PRECAUTIONS**—*Renal Effects*). *In vitro* studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding site other drugs which are also albumin-bound (see **CLINICAL PHARMACOLOGY**—PHARMACOKINETICS).
Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.
Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin,

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 has also been reported. Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.
Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.
Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen, naproxen sodium and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.
DRUG/LABORATORY TEST INTERACTIONS
Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined. 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-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.
Naproxen may interfere with some urinary assays of 5-hydroxyindoleacetic acid (5HIAA).
CARCINOGENESIS
A two year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8 mg/kg/day, 16 mg/kg/day, and 24 mg/kg/day (50 mg/m^2, 100 mg/m^2, and 150 mg/m^2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.
PREGNANCY
Teratogenic Effects: Pregnancy Category B
Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure) rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure) and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Naprelan should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.
Nonteratogenic Effects
There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in the late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during third trimester should be avoided.
NURSING MOTHERS
The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.
PEDIATRIC USE
No pediatric studies have been performed with Naprelan, thus safety of Naprelan in pediatric populations has not been established.

ADVERSE REACTIONS

As with all drugs in this class, the frequency and severity of adverse events depends on several factors: the dose of the drug and duration of treatment; the age, the sex, physical condition of the patient; any concurrent medical diagnoses or individual risk factors.
The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between drug usage and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least one case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.
The adverse reactions reported were based on the results from two double-blind controlled clinical trials of three months duration with an additional nine month open-label extension. A total of 542 patients received Naprelan either in the double-blind period or in the nine month open-label extension. Of these 542 patients, 232 received Naprelan, 167 were initially treated with Naprosyn and 143 were initially treated with placebo. Adverse reactions reported by patients who received Naprelan are shown by body system. Those adverse reactions observed with naproxen but not reported in controlled trials with Naprelan are italicized.

by dyspepsia (14%), and flu syndrome (10%). The incidence of other adverse events occurring in 3%–9% of the patients are marked with an asterisk.
Those reactions occurring in less than 3% of the patients are unmarked.
INCIDENCE GREATER THAN 1% (PROBABLE CAUSAL RELATIONSHIP)
Body as a Whole—Pain (back)*, pain*, infection*, fever, injury (accident), asthenia, pain chest, headache (15%), flu syndrome (10%).
Gastrointestinal—Nausea*, diarrhea*, constipation*, abdominal pain*, flatulence, gastritis, vomiting, dysphagia, dyspepsia (14%), *heartburn*, stomatitis.*
Hematologic—Anemia, ecchymosis.
Respiratory—Pharyngitis*, rhinitis*, sinusitis*, bronchitis, cough increased.
Renal—Urinary tract infection*, cystitis.
Dermatologic—Skin rash*, *skin eruptions*, ecchymoses*, purpura.*
Metabolic and Nutrition—Peripheral edema, hyperglycemia.
Central Nervous System—Dizziness, paresthesia, insomnia, *drowsiness*, lightheadedness.*
Cardiovascular—Hypertension, *edema*, dyspnea*, palpitations.*
Musculoskeletal—Cramps (leg), myalgia, arthralgia, joint disorder, tendon disorder.
Special Senses—*Tinnitus*, hearing disturbances, visual disturbances.*
General—*Thirst.*
INCIDENCE LESS THAN 1% (PROBABLE CAUSAL RELATIONSHIP)
Body as a Whole—Abscess, monilia, neck rigid, pain neck, abdomen enlarged, carcinoma, cellulitis, edema general, LE syndrome, malaise, mucous membrane disorder, allergic reaction, pain pelvic.
Gastrointestinal—Anorexia, cholecystitis, cholelithiasis, eructation, GI hemorrhage, rectal hemorrhage, stomatitis aphthous, stomatitis ulcer, ulcer mouth, ulcer stomach, periodontal abscess, cardiospasm, colitis, esophagitis, gastroenteritis, GI disorder, rectal disorder, tooth disorder, hepatosplenomegaly, liver function abnormality, melena, ulcer esophagus, *hematemesis, jaundice, pancreatitis, necrosis.*
Renal—Dysmenorrhea, dysuria, kidney function abnormality, nocturia, prostate disorder, pyelonephritis, carcinoma breast, urinary incontinence, kidney calculus, kidney failure, menorrhagia, metrorrhagia, neoplasm breast, nephrosclerosis, hematuria, pain kidney, pyuria, urine abnormal, urinary frequency, urinary retention, uterine spasm, vaginitis, *glomerular nephritis, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.*
Hematologic—Leukopenia, bleeding time increased, eosinophilia, abnormal RBC, abnormal WBC, thrombocytopenia, *agranulocytosis, granulocytopenia.*
Central Nervous System—Depression, anxiety, hypertonia, nervousness, neuralgia, neuritis, vertigo, amnesia, confusion, co-ordination, abnormal diplopia, emotional lability, hematoma subdural, paralysis, *dream abnormalities, inability to concentrate, muscle weakness.*
Dermatologic: Angiodermatitis, herpes simplex, dry skin, sweating, ulcer skin, acne, alopecia, dermatitis contact, eczema, herpes zoster, nail disorder, skin necrosis, subcutaneous nodule, pruritis, urticaria, neoplasm skin, *photosensitive dermatitis, photosensitivity reactions resembling porphyria cutaneous tarda, epidermolysis bullosa.*
Special Senses—Amblyopia scleritis, cataract, conjunctivitis, deaf, ear disorder, keratoconjunctivitis, lacrimation disorder, otitis media, pain eye.
Cardiovascular—Angina pectoris, coronary artery disease, myocardial infarction, deep thrombophlebitis, vasodilation, vascular anomaly, arrhythmia, bundle branch block, abnormal ECG, heart failure right, hemorrhage, migraine, aortic stenosis, syncope, tachycardia, *congestive heart failure.*
Respiratory—Asthma, dyspnea, lung edema, laryngitis, lung disorder, epistaxis, pneumonia, respiratory distress, respiratory disorder, *eosinophilic pneumonitis.*
Musculoskeletal—Myasthenia, bone disorder, spontaneous bone fracture, fibrotendinitis, bone pain, ptosis, spasm general, bursitis.
Metabolic and Nutrition—Creatinine increase, glucosuria, hypercholesteremia, albuminuria, alkalosis, BUN increased, dehydration, edema, glucose tolerance decrease, hyperuricemia, hypokalemia, SGOT increase, SGPT increase, weight decrease.
General—*Anaphylactoid reactions, angioneurotic edema, menstrual disorders, hypoglycemia, pyrexia (chills and fevers).*
INCIDENCE LESS THAN 1% (CAUSAL RELATIONSHIP UNKNOWN)
Other adverse reactions listed in the naproxen package label, but not reported by those who received Naprelan are shown in italics. These observations are being listed as
Central Nervous System: *Aseptic meningitis, cognitive dysfunction.*
Dermatologic—*Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.*
Gastrointestinal—*Non-peptic GI ulceration, ulcerative stomatitis.*
Cardiovascular—*Vasculitis.*

OVERDOSAGE

Significant naproxen overdosage may be characterized by drowsiness, heartburn, indigestion, nausea, or vomiting. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 500 mg/kg in rats, 1200 mg/kg in mice, 4000 mg/kg in hamsters and greater than 1000 mg/kg in dogs.
Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

DOSAGE AND ADMINISTRATION

RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, AND ANKYLOSING SPONDYLITIS
The usual daily dose of Naprelan is two Naprelan 375 mg tablets (750 mg) once daily, or two Naprelan 500 mg tablets (1000 mg) once a day. Both larger and smaller doses may be required in individual patients (see **Individualization of Dosage**). Regardless of indication, the dosage should be individualized to achieve effective dose and minimize adverse events, however the maximum daily dose is three Naprelan 500 mg once daily.
MANAGEMENT OF PAIN, PRIMARY DYSMENORRHEA, AND ACUTE TENDINITIS AND BURSITIS
The recommended starting dose is two Naprelan 500 mg tablets (1000 mg) once daily. For patients requiring greater analgesic benefit, three Naprelan 500 mg tablets (1500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two Naprelan 500 mg tablets (1000 mg).
ACUTE GOUT
The recommended dose on the first day is two to three Naprelan 500 mg tablets (1000–1500 mg) once daily, followed by two Naprelan 500 mg tablets (1000 mg) once daily, until the attack has subsided.

HOW SUPPLIED

Naprelan® (naproxen sodium) Controlled Release Tablets are available as follows:
Naprelan 375: white, capsule-shaped tablet with "W" on one side and "901" on the reverse; in bottles of 100; NDC 0008-0901-03. Each tablet contains 412.5 mg naproxen sodium equivalent to 375 mg naproxen.
Naprelan 500: white, capsule-shaped tablet with "W" on one side and "902" on the reverse; in bottles of 75; NDC 0008-0902-02. Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.
Caution: Federal law prohibits dispensing without prescription.
US Patent Pending.

Store at controlled room temperature, 20°–25° C (68°–77° F).
Dispense in a well-closed container.
Manufactured for
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101
by
élan pharma ltd.
Athlone, Ireland
Shown in Product Identification Guide, page 344

NORDETTE®–21 ℞

[nŏr-dĕt '-21]
TABLETS
(levonorgestrel and ethinyl estradiol tablets)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

ORAL CONTRACEPTIVE
Each Nordette tablet contains 0.15 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5 (10)-trien-20-yne-3,17-diol). The inactive ingredients present are cellu-

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.
Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization and the IUD, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I: LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD
% of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use

Method	Lowest Expected*	Typical**
(No Contraception)	(85)	(85)
Oral contraceptives		3
combined	0.1	N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foams and vaginal suppositories)	3	21
Vaginal Sponge		
nulliparous	6	18
multiparous	9	28
DEPO-PROVERA® (injectable progestogen)	0.3	0.3
NORPLANT® SYSTEM (implants)	0.2#	0.2#
IUD		3
progesterone	2	N/A***
copper T 380A	0.8	N/A***
Condom without spermicides	2	12
Periodic abstinence (all methods)	1–9	20
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15

Adapted from J. Trussell et al., Table 1, Studies in Family Planning, *21(1)*. Jan.–Feb. 1990.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop use for any other reason.
** This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
*** N/A—Data not available
\# This data is based on NORPLANT® SYSTEM clinical trials.

CONTRAINDICATIONS

Oral contraceptives should not be used in women with any of the following conditions:
Thrombophlebitis or thromboembolic disorders.
A past history of deep-vein thrombophlebitis or thromboembolic disorders.
Cerebral-vascular or coronary-artery disease.
Known or suspected carcinoma of the breast.
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
Undiagnosed abnormal genital bleeding.
Cholestatic jaundice of pregnancy or jaundice with prior pill use.
Hepatic adenomas or carcinomas.
Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite