PDR®
48
EDITION
1994

PHYSICIANS' DESK REFERENCE®

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ISBN: 1-56363-061-3

ace areas, prolonged use, the addition of occlusive dressings, and dosage form.
Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.
Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.
Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use).
Not for ophthalmic use. Severe irritation is possible if fluocinonide solution contacts the eye. If that should occur, immediate flushing of the eye with a large volume of water is recommended.
If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.
As with any topical corticosteroid product, prolonged use may produce atrophy of the skin and subcutaneous tissues. When used on intertriginous or flexor areas, or on the face, this may occur even with short-term use.
In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
As with all antibiotics, prolonged use of NEO-SYNALAR may result in over-growth of nonsusceptible organisms. If superinfection occurs, appropriate measures should be taken.
SYNALAR-HP cream should not be used for prolonged periods and the quantity per day should not exceed 2 g. of formulated material.

Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes. If there is contact with the eyes and severe irritation occurs, immediately flush with a large volume of water.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating HPA axis suppression: Urinary free cortisol test and ACTH stimulation test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.
Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: SYNALAR-HP cream 0.2% should not be used on infants up to 2 years of age.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.
Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria. The following reactions have been reported with the topical use of neomycin: ototoxicity and nephrotoxicity.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (See PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Topical corticosteroids are generally applied to the affected area as a thin film from two to four times daily depending on the severity of the condition. In hairy sites, the hair should be parted to allow direct contact with the lesion.
Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. Some plastic films may be flammable and due care should be exercised in their use. Similarly, caution should be employed when such films are used on children or left in their proximity, to avoid the possibility of accidental suffocation.
If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED

LIDEX® (fluocinonide) cream 0.05%—15 g Tube (NDC 0033-2511-13), 30 g Tube (NDC 0033-2511-14), 60 g Tube (NDC 0033-2511-17), and 120 g Tube (NDC 0033-2511-22). Store at room temperature. Avoid excessive heat, above 40°C (104°F).
LIDEX® (fluocinonide) gel 0.05%—15 g Tube (NDC 0033-2507-13), 30 g Tube (NDC 0033-2507-14), 60 g Tube (NDC 0033-2507-17), and 120 g Tube (NDC 0033-2507-22). Store at controlled room temperature, 15–30°C (59–86°F).
LIDEX® (fluocinonide) ointment 0.05%—15 g Tube (NDC 0033-2514-13), 30 g Tube (NDC 0033-2514-14), 60 g Tube (NDC 0033-2514-17), and 120 g Tube (NDC 0033-2514-22). Store at room temperature. Avoid temperature above 30°C (86°F).
LIDEX® (fluocinonide) topical solution 0.05%—Plastic squeeze bottles: 20 cc (NDC 0033-2517-44) and 60 cc (NDC 0033-2517-46). Store at room temperature. Avoid excessive heat, above 40°C (104°F).
LIDEX-E® (fluocinonide) cream 0.05%—15 g Tube (NDC 0033-2513-13), 30 g Tube (NDC 0033-2513-14), 60 g Tube (NDC 0033-2513-17), and 120 g Tube (NDC 0033-2513-22). Store at room temperature. Avoid excessive heat, above 40°C (104°F).
NEO-SYNALAR® cream—15 g Tube (NDC 0033-2505-13), 30 g Tube (NDC 0033-2505-14), 60 g Tube (NDC 0033-2505-17). Store at room temperature. Avoid freezing and excessive heat, above 40°C (104°F).
SYNACORT® (hydrocortisone) cream 1%—15 g Tube (NDC 0033-2519-13), 30 g Tube (NDC 0033-2519-14), and 60 g Tube (NDC 0033-2519-17). SYNACORT® (hydrocortisone) cream 2.5%—30 g Tube (NDC 0033-2520-14). Store at room temperature. Avoid excessive heat, above 40°C (104°F).
SYNALAR® (fluocinolone acetonide) cream 0.025%—15 g Tube (NDC 0033-2501-13), 30 g Tube (NDC 0033-2501-14), 60 g Tube (NDC 0033-2501-17), and 425 g Jar (NDC 0033-2501-23). Store tubes at room temperature. Avoid freezing and excessive heat, above 40°C (104°F). Store jars at controlled room temperature, 15°–30°C (59°–86°F).
SYNALAR® (fluocinolone acetonide) cream 0.01%—15 g Tube (NDC 0033-2502-13), 30 g Tube (NDC 0033-2502-14), 60 g Tube (NDC 0033-2502-17), and 425 g Jar (NDC 0033-2502-23). Store tubes at room temperature. Avoid freezing and excessive heat, above 40°C (104°F). Store jars at controlled room temperature, 15°–30°C (59°–86°F).
SYNALAR® (fluocinolone acetonide) ointment 0.025%—15 g Tube (NDC 0033-2504-13), 30 g Tube (NDC 0033-2504-14), 60 g Tube (NDC 0033-2504-17), and 425 g Jar (NDC 0033-2504-23). Store at room temperature. Avoid excessive heat, above 40°C (104°F).
SYNALAR® (fluocinolone acetonide) topical solution 0.01%—20 cc (NDC 0033-2506-44) and 60 cc (NDC 0033-2506-46). Store at room temperature. Avoid freezing.
SYNEMOL® (fluocinolone acetonide) cream 0.025%—15 g Tube (NDC 0033-2509-13), 30 g Tube (NDC 0033-2509-14), 60 g Tube (NDC 0033-2509-17). Store at room temperature. Avoid excessive heat, above 40°C (104°F).
CAUTION: Federal law prohibits dispensing without a prescription.
LIDEX ointment: U.S. Patent No. 4,017,615

Revised 4/91

NAPROSYN®

[*nă 'pro-sin*]
(naproxen)
Tablets and Suspension

Products of Syntex Puerto Rico, Inc.

DESCRIPTION

NAPROSYN® (naproxen) tablets for oral administration each contain 250 mg, 375 mg or 500 mg of naproxen. NAPROSYN suspension for oral administration contains 125 mg/5 mL of naproxen. NAPROSYN is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.
The chemical name for naproxen is 2-naphthaleneacetic acid, 6-methoxy-α-methyl-,(+).
Naproxen is an odorless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH.
Each tablet contains naproxen, the active ingredient, with the following inactive ingredients: Croscarmellose sodium, iron oxides, magnesium stearate and povidone.
NAPROSYN suspension for oral administration contains 125 mg/5 mL of naproxen, the active ingredient, in a vehicle of FD&C Yellow #6, fumaric acid, imitation orange flavor, imitation pineapple flavor, magnesium aluminum silicate, methylparaben, purified water, sodium chloride, sorbitol solution and sucrose.

CLINICAL PHARMACOLOGY

NAPROSYN (naproxen) is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Naproxen sodium, the sodium salt of naproxen, has been developed as an analgesic because it is more rapidly absorbed. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.
Naproxen is rapidly and completely absorbed from the gastrointestinal tract. After administration of naproxen, peak plasma levels of naproxen anion are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4–5 doses. The mean biological half-life of the anion in humans is approximately 13 hours, and at therapeutic levels it is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day there is a lack of dose proportionality due to an increase in clearance caused by saturation of proteins at higher doses. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-0-desmethyl naproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes.
In children of 5 to 16 years of age with arthritis, plasma naproxen levels following a 5 mg/kg single dose of suspension were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in children and adults. Pharmacokinetic studies of naproxen were not performed in children of less than 5 years of age.
The drug was studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout. It is not a corticosteroid. Improvement in patients treated for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time.
In patients with osteoarthritis, the therapeutic action of the drug has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.
In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, the drug has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less than in both the aspirin- and indomethacin-treated

Syntex—Cont.

patients. It is not known whether the drug causes less peptic ulceration than aspirin.
In patients with ankylosing spondylitis, the drug has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.
In patients with acute gout, a favorable response to the drug was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24–48 hours, as well as by relief of pain and tenderness.
The drug may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether the drug could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts the drug did result in greater improvement. Its use in combination with salicylates is not recommended because data are inadequate to demonstrate that the drug produces greater improvement over that achieved with aspirin alone. Further, there is some evidence that aspirin increases the rate of excretion of the drug.
Generally, improvement due to the drug has not been found to be dependent on age, sex, severity or duration of disease.
In clinical trials in patients with osteoarthritis and rheumatoid arthritis comparing treatments of 750 mg per day with 1,500 mg per day, there were trends toward increased efficacy with the higher dose and a more clearcut increase in adverse reactions, particularly gastrointestinal reactions severe enough to cause the patient to leave the trial, which approximately doubled.
The drug was studied in patients with mild to moderate pain, and pain relief was obtained within 1 hour. It is not a narcotic and is not a CNS-acting drug. Controlled double-blind studies have demonstrated the analgesic properties of the drug in, for example, post-operative, post-partum, orthopedic and uterine contraction pain and dysmenorrhea. In dysmenorrheic patients, the drug reduces the level of prostaglandins in the uterus, which correlates with a reduction in the frequency and severity of uterine contractions. Analgesic action has been shown by such measures as a reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time for required remedication. The analgesic effect has been found to last for up to 7 hours.
In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of the drug has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

The drug is contraindicated in patients who have had allergic reactions to NAPROSYN® (naproxen), ANAPROX® (naproxen sodium) or ANAPROX® DS (naproxen sodium). It is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to NAPROSYN, ANAPROX, or ANAPROX DS, 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.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy:
Serious gastrointestinal 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 gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross tients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.
Studies to date have not identified any subset of patients not at risk of developing 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:
***NAPROSYN* (NAPROXEN) SHOULD NOT BE USED CONCOMITANTLY WITH THE RELATED DRUG *ANAPROX* OR *ANAPROX DS* (NAPROXEN SODIUM) SINCE THEY BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION.**
Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.
A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a 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, 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.
NAPROSYN and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. 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.
Chronic alcoholic liver disease and probably 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. It is prudent to use the lowest effective dose.
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.
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. 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 this drug. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.
If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.
Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically.
Peripheral edema has been observed in some patients. For this reason, the drug should be used with caution in patients with fluid retention, hypertension or heart failure.
The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions.
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.
Information for Patients:
Naproxen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.
NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) 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 sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.
Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with the drug.
Laboratory Tests:
Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy).
Drug Interactions:
In vitro studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound. 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.
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.
This and other nonsteroidal anti-inflammatory drugs 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 this drug is administered concomitantly with methotrexate. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly enhancing the toxicity of that drug.
Drug/Laboratory Test Interactions:
The drug may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.
The administration of the drug 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 the drug be temporarily discontinued 72 hours before adrenal function tests are performed.
The drug may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).
Carcinogenesis:
A two-year study was performed in rats to evaluate the carcinogenic potential of the drug. No evidence of carcinogenicity was found.
Pregnancy:
Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats, rabbits and mice at doses up to six times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to the drug. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should not be used during pregnancy unless clearly needed. 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.
Non-teratogenic Effects: As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats.
Nursing Mothers:
The naproxen anion has been found in the milk of lactating

aglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use:
Safety and effectiveness in children below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see Dosage and Administration). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5–5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age.

ADVERSE REACTIONS

The following adverse reactions are divided into 3 parts based on frequency and likelihood of causal relationship to naproxen.

Incidence greater than 1%

Probable Causal Relationship:
Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, these reactions were reported 2 to 10 times more frequently than they were in studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea.
A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking 1,500 mg naproxen daily compared to those taking 750 mg daily (see Clinical Pharmacology).
In controlled clinical trials with about 80 children and in well-monitored open studies with about 400 children with juvenile arthritis, the incidences of rash and prolonged bleeding times were increased, the incidences of gastrointestinal and central nervous system reactions were about the same, and the incidences of other reactions were lower in children than in adults.
Gastrointestinal: The most frequent complaints reported related to the gastrointestinal tract. They were: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, stomatitis.
Central Nervous System: Headache*, dizziness*, drowsiness*, lightheadedness, vertigo.
Dermatologic: Itching (pruritus)*, skin eruptions*, ecchymoses*, sweating, purpura.
Special Senses: Tinnitus*, hearing disturbances, visual disturbances.
Cardiovascular: Edema*, dyspnea*, palpitations.
General: Thirst.

Incidence less than 1%

Probable Causal Relationship:
The following adverse reactions were reported less frequently than 1% during controlled clinical trials and through voluntary reports since marketing. The probability of a causal relationship exists between the drug and these adverse reactions:
Gastrointestinal: Abnormal liver function tests, colitis, gastrointestinal bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting.
Renal: Glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.
Hematologic: Agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia.
Central Nervous System: Depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness.
Dermatologic: Alopecia, photosensitive dermatitis, skin rashes.
Special Senses: Hearing impairment.
Cardiovascular: Congestive heart failure.
Respiratory: Eosinophilic pneumonitis.
General: Anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever).

Causal Relationship Unknown:
Other reactions have been reported in circumstances in which a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to the physicians:
Hematologic: Aplastic anemia, hemolytic anemia.
Central Nervous System: Aseptic meningitis, cognitive dysfunction.
Dermatologic: Epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria.
Gastrointestinal: Non-peptic gastrointestinal ulceration, ulcerative stomatitis.
Cardiovascular: Vasculitis.
General: Angioneurotic edema, hyperglycemia, hypoglycemia.

OVERDOSAGE

Significant overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. 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 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.
Should a patient ingest a large number of tablets or a large volume of suspension, 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

A measuring cup marked in ½ teaspoon and 2.5 milliliter increments is provided with the suspension. This cup or a teaspoon may be used to measure the appropriate dose.
For Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis:
The recommended dose of NAPROSYN® (naproxen) in adults is 250 mg (10 mL or 2 tsp of suspension), 375 mg (15 mL or 3 tsp), or 500 mg (20 mL or 4 tsp) twice daily (morning and evening). During long-term administration, the dose may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary. In patients who tolerate lower doses well, the dose may be increased to 1,500 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with the 1,500 mg/day dose, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see Clinical Pharmacology).
Symptomatic improvement in arthritis usually begins within 2 weeks. However, if improvement is not seen within this period, a trial for an additional 2 weeks should be considered.
For Juvenile Arthritis:
The recommended total daily dose of NAPROSYN is approximately 10 mg/kg given in 2 divided doses. One half of the 250 mg tablet may be used to approximate this dose. The following table may be used as a guide for the suspension:

Child's Weight	Dose
13 kg (29 lb)	2.5 mL (½ tsp) b.i.d.
25 kg (55 lb)	5 mL (1 tsp) b.i.d.
38 kg (84 lb)	7.5 mL (1½ tsp) b.i.d.

For Acute Gout:
The recommended starting dose of NAPROSYN is 750 mg (30 mL or 6 tsp), followed by 250 mg (10 mL or 2 tsp) every 8 hours until the attack has subsided.
For Mild to Moderate Pain, Primary Dysmenorrhea and Acute Tendinitis and Bursitis:
The recommended starting dose of NAPROSYN is 500 mg (20 mL or 4 tsp), followed by 250 mg (10 mL or 2 tsp) every 6 to 8 hours as required. The total daily dose should not exceed 1,250 mg (50 mL or 10 tsp).

HOW SUPPLIED

NAPROSYN® (naproxen) is available as yellow 250 mg tablets in light-resistant bottles of 100 tablets (NDC 18393-272-42) (NSN 6505-01-026-9730) and 500 tablets (NDC 18393-272-62) (NSN 6505-01-046-0126) or in cartons of 100 individually blister-packed tablets (NDC 18393-272-53) (NSN 6505-01-097-9611). Peach 375 mg tablets are available in light-resistant bottles of 100 tablets (NDC 18393-273-42) (NSN 6505-01-135-8462) and 500 tablets (NDC 18393-273-62) (NSN 6505-01-204-5297) or in cartons of 100 individually blister-packed tablets (NDC 18393-273-53) (NSN 6505-01-204-5298). Yellow 500 mg tablets are available in light-resistant bottles of 100 tablets (NDC 18393-277-42) (NSN 6505-01-200-2474) and 500 tablets (NDC 18393-277-62) (NSN 6505-01-186-8758) or in cartons of 100 individually blister-packed tablets (NDC 18393-277-53). Store at room temperature in well-closed containers; dispense in light-resistant containers.
NAPROSYN® suspension is available in 1 pint (474 mL) light-resistant bottles (NDC 18393-278-20). Measuring cups are provided so that one can be dispensed with each prescription. Store at room temperature; avoid excessive heat, above 40°C (104° F). Dispense in light-resistant container.
CAUTION: Federal law prohibits dispensing without prescription.
U.S. Patent Nos. 3,904,682; 3,998,966 and others.
Revised 9/90

NASALIDE®

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[na'zăl-lide]
(flunisolide)
Nasal Solution
0.025%
For Nasal Use Only

A product of Syntex Laboratories, Inc.

DESCRIPTION

NASALIDE® (flunisolide) nasal solution is intended for administration as a spray to the nasal mucosa. Flunisolide, the active component of NASALIDE nasal solution, is an anti-inflammatory steroid with the chemical name: 6α-fluoro-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone (USAN).
Flunisolide is a white to creamy white crystalline powder with a molecular weight of 434.49. It is soluble in acetone, sparingly soluble in chloroform, slightly soluble in methanol, and practically insoluble in water. It has a melting point of about 245°C.
Each 25 mL spray bottle contains flunisolide 6.25 mg (0.25 mg/mL) in a solution of propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride, and purified water, with NaOH and/or HCl added to adjust the pH to approximately 5.3. It contains no fluorocarbons.
After priming the delivery system for NASALIDE, each actuation of the unit delivers a metered droplet spray containing approximately 25 mcg of flunisolide. The size of the droplets produced by the unit is in excess of 8 microns to facilitate deposition on the nasal mucosa. The contents of one nasal spray bottle deliver at least 200 sprays.

CLINICAL PHARMACOLOGY

NASALIDE® (flunisolide) has demonstrated potent glucocorticoid and weak mineralocorticoid activity in classical animal test systems. As a glucocorticoid it is several hundred times more potent than the cortisol standard. Clinical studies with flunisolide have shown therapeutic activity on nasal mucous membranes with minimal evidence of systemic activity at the recommended doses.
A study in approximately 100 patients which compared the recommended dose of flunisolide nasal solution with an oral dose providing equivalent systemic amounts of flunisolide has shown that the clinical effectiveness of NASALIDE, when used topically as recommended, is due to its direct local effect and not to an indirect effect through systemic absorption.
Following administration of flunisolide to man, approximately half of the administered dose is recovered in the urine and half in the stool; 65–70% of the dose recovered in urine is the primary metabolite, which has undergone loss of the 6α fluorine and addition of a 6β hydroxy group. Flunisolide is well absorbed but is rapidly converted by the liver to the much less active primary metabolite and to glucuronate and/or sulfate conjugates. Because of first-pass liver metabolism, only 20% of the flunisolide reaches the systemic circulation when it is given orally whereas 50% of the flunisolide administered intranasally reaches the systemic circulation unmetabolized. The plasma half-life of flunisolide is 1–2 hours.
The effects of flunisolide on hypothalamic-pituitary-adrenal (HPA) axis function have been studied in adult volunteers. NASALIDE was administered intranasally as a spray in total doses over 7 times the recommended dose (2200 mcg, equivalent to 88 sprays/day) in 2 subjects for 4 days, about 3 times the recommended dose (800 mcg, equivalent to 32 sprays/day) in 4 subjects for 4 days, and over twice the recommended dose (700 mcg, equivalent to 28 sprays/day) in 6 subjects for 10 days. Early morning plasma cortisol concentrations and 24-hour urinary 17-ketogenic steroids were measured daily. There was evidence of decreased endogenous cortisol production at all three doses.
In controlled studies, NASALIDE was found to be effective in reducing symptoms of stuffy nose, runny nose and sneezing in most patients. These controlled clinical studies have been conducted in 488 adult patients at doses ranging from 8 to 16 sprays (200–400 mcg) per day and 127 children at doses ranging from 6 to 8 sprays (150–200 mcg) per day for periods as long as 3 months. In 170 patients who had cortisol levels evaluated at baseline and after 3 months or more of flunisolide treatment, there was no unequivocal flunisolide-related depression of plasma cortisol levels.
The mechanisms responsible for the anti-inflammatory action of corticosteroids and for the activity of the aerosolized drug on the nasal mucosa are unknown.

INDICATIONS

NASALIDE® (flunisolide) is indicated for the topical treatment of the symptoms of seasonal or perennial rhinitis when effectiveness of or tolerance to conventional treatment is unsatisfactory.
Clinical studies have shown that improvement is based on a local effect rather than systemic absorption, and is usually