PDR®

54

EDITION

2000

PHYSICIANS' DESK REFERENCE®

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Dose	Shape	Bottle	Tel-E-Dose
5 mg	oval	NDC 0004-0262-01	NDC 0004-0262-49
10 mg	oval	NDC 0004-0263-01	NDC 0004-0263-49
20 mg	oval	NDC 0004-0264-01	NDC 0004-0264-49
100 mg	capsule-shaped	NDC 0004-0265-01	NDC 0004-0265-49

Angioedema has been reported in a patient exposed to DEMADEX who was later found to be allergic to sulfa drugs.

Of the adverse reactions during placebo-controlled trials listed without taking into account assessment of relatedness to drug therapy, arthritis and various other nonspecific musculoskeletal problems were more frequently reported in association with DEMADEX than with placebo, even though gout was somewhat more frequently associated with placebo. These reactions did not increase in frequency or severity with the dose of DEMADEX. One patient in the group treated with DEMADEX withdrew due to myalgia, and one in the placebo group withdrew due to gout.

Hypokalemia. See WARNINGS.

OVERDOSAGE

There is no human experience with overdoses of DEMADEX, but the signs and symptoms of overdosage can be anticipated to be those of excessive pharmacologic effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and hemoconcentration. Treatment of overdosage should consist of fluid and electrolyte replacement.

Laboratory determinations of serum levels of torsemide and its metabolites are not widely available.

No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of torsemide and its metabolites. Torsemide is not dialyzable, so hemodialysis will not accelerate elimination.

DOSAGE AND ADMINISTRATION

General: DEMADEX tablets may be given at any time in relation to a meal, as convenient. Special dosage adjustment in the elderly is not necessary.

Because of the high bioavailability of DEMADEX, oral and intravenous doses are therapeutically equivalent, so patients may be switched to and from the intravenous form with no change in dose. DEMADEX intravenous injection should be administered either slowly as a bolus over a period of 2 minutes or administered as a continuous infusion.

If DEMADEX is administered through an IV line, it is recommended that, as with other IV injections, the IV line be flushed with Normal Saline (Sodium Chloride Injection, USP) before and after administration. DEMADEX injection is formulated above pH 8.3. Flushing the line is recommended to avoid the potential for incompatibilities caused by differences in pH which could be indicated by color change, haziness or the formation of a precipitate in the solution.

If DEMADEX is administered as a continuous infusion, stability has been demonstrated through 24 hours at room temperature in plastic containers for the following fluids and concentrations:

200 mg DEMADEX (10 mg/mL) added to:
- 250 mL Dextrose 5% in water
- 250 mL 0.9% Sodium Chloride
- 500 mL 0.45% Sodium Chloride

50 mg DEMADEX (10 mg/mL) added to:
- 500 mL Dextrose 5% in water
- 500 mL 0.9% Sodium Chloride
- 500 mL 0.45% Sodium Chloride

Before administration, the solution of DEMADEX should be visually inspected for discoloration and particulate matter. If either is found, the ampul should not be used.

Congestive Heart Failure: The usual initial dose is 10 mg or 20 mg of once-daily oral or intravenous DEMADEX. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

Chronic Renal Failure. The usual initial dose of DEMADEX is 20 mg of once-daily oral or intravenous DEMADEX. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

Hepatic Cirrhosis: The usual initial dose is 5 mg or 10 mg of once-daily oral or intravenous DEMADEX, administered together with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 40 mg have not been adequately studied.

Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.

Hypertension: The usual initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4 to 6 weeks, the dose may be increased to 10 mg once daily. If the response to 10 mg is insufficient, an additional antihypertensive agent should be added to the treatment regimen.

HOW SUPPLIED

DEMADEX for oral administration is available as white, scored tablets containing 5 mg, 10 mg, 20 mg, or 100 mg of torsemide. The tablets are supplied in bottles and Tel-E-Dose®* packages of 100 as follows:

[See table above]

Each tablet is debossed on the scored side with the mg, 10 mg, 20 mg, or 100 mg, respectively). On the opposite side, the tablet is debossed with 5, 10, 20, or 100 to indicate the dose.

DEMADEX for intravenous injection is supplied in clear ampuls containing 2 mL (20 mg, NDC 0004-0267-06) or 5 mL (50 mg, NDC 0004-0268-06) of a 10 mg/mL sterile solution.

Storage: Store all dosage forms at 15° to 30°C (59° to 86°F). Do not freeze.

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*Tel-E-Dose is a registered trademark of Hoffmann-La Roche Inc.

Tablets manufactured by:
Boehringer Mannheim, GmbH, Mannheim, Germany
Ampuls manufactured by:
Abbott Laboratories, North Chicago, IL 60064

Revised: April 1998

Shown in Product Identification Guide, page 334

EC-NAPROSYN® ℞
(naproxen)
Delayed-Release Tablets

NAPROSYN® ℞
(naproxen)
Tablets

ANAPROX®/ANAPROX® DS ℞
[*an' ă-prox*]
(naproxen sodium)
Tablets

NAPROSYN® ℞
(naproxen)
Suspension

The following text is complete prescribing information based on official labeling in effect June 1999.

DESCRIPTION

Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical names for naproxen and naproxen sodium are (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt, respectively.

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. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

NAPROSYN (naproxen) Tablets contain 250 mg, 375 mg or 500 mg of naproxen and croscarmellose sodium, iron oxides, povidone and magnesium stearate.

EC-NAPROSYN (naproxen) Delayed-Release Tablets are enteric-coated tablets containing 375 mg or 500 mg of naproxen and croscarmellose sodium, povidone and magnesium stearate. The enteric coating dispersion contains methacrylic acid copolymer, talc, triethyl citrate, sodium hydroxide and purified water. The dispersion may also contain simethicone emulsion. The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

Each ANAPROX 275 mg and ANAPROX DS 550 mg tablet contains naproxen sodium, the active ingredient, with magnesium stearate, microcrystalline cellulose, povidone and talc. The coating suspension for the ANAPROX 275 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4210A, polyethylene glycol 8000 or Opadry YS-1-4215. The coating suspension for the ANAPROX DS 550 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4227, polyethylene glycol 8000 or Opadry YS-1-4216.

NAPROSYN (naproxen) Suspension for oral administration contains 125 mg/5 mL of naproxen in a vehicle containing sucrose, magnesium aluminum silicate, sorbitol solution and sodium chloride (30 mg/5 mL, 1.5 mEq), methylparaben, fumaric acid, FD&C Yellow No. 6, imitation pineapple flavor, imitation orange flavor and purified water. The pH of the suspension ranges from 2.2 to 3.7.

CLINICAL PHARMACOLOGY

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Pharmacokinetics: Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C_{max}); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption:

Immediate Release: After administration of NAPROSYN tablets, peak plasma levels are attained in 2 to 4 hours. After oral administration of ANAPROX, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in ANAPROX. Peak plasma levels of naproxen given as NAPROSYN Suspension are attained in 1 to 4 hours.

Delayed Release: EC-NAPROSYN is designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for EC-NAPROSYN dissolves above pH 6. When EC-NAPROSYN was given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours). An in vivo study in man using radiolabeled EC-NAPROSYN tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine rather than the stomach, so the absorption of the drug is delayed until the stomach is emptied. When EC-NAPROSYN and NAPROSYN were given to fasted subjects (n=24) in a crossover study following 1 week of dosing, differences in time to peak plasma levels (T_{max}) were observed, but there were no differences in total absorption as measured by C_{max} and AUC:

[See table at top of next page]

Antacid Effects: When EC-NAPROSYN was given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with antacid 5 hours), although not significantly.

Food Effects: When EC-NAPROSYN was given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (T_{max}), but did not affect peak naproxen levels (C_{max}).

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 less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism:

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

Elimination:

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations:

Pediatric Patients: In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see DOSAGE AND ADMINISTRATION) 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 pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients. EC-NAPROSYN has not been studied in subjects under the age of 18.

Renal Insufficiency. Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

CLINICAL STUDIES

General Information: Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling,

EC-Naprosyn/Anaprox—Cont.

	EC-NAPROSYN* 500 mg bid	NAPROSYN* 500 mg bid
C_{max} (µg/mL)	94.9 (18%)	97.4 (13%)
T_{max} (hours)	4 (39%)	1.9 (61%)
AUC_{0-12hr} (µg-hr/mL)	845 (20%)	767 (15%)

* Mean value (coefficient of variation)

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. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis

In patients with osteoarthritis, the therapeutic action of naproxen 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.

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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 in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen 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 naproxen was shown by significant clearing of inflammatory changes (eg, decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen and within 30 minutes in patients taking naproxen sodium Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen 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 naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates 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.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen as 1000 mg of NAPROSYN (naproxen) or 1100 mg of ANAPROX (naproxen sodium) has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Three 6-week, double-blind, multicenter studies with EC-NAPROSYN (naproxen) (375 or 500 mg bid, n=385) and NAPROSYN (375 or 500 mg bid, n=279) were conducted comparing EC-NAPROSYN with NAPROSYN, including 355 rheumatoid arthritis and osteoarthritis patients who had a recent history of NSAID-related GI symptoms. These studies indicated that EC-NAPROSYN and NAPROSYN showed no significant differences in efficacy or safety and had similar prevalence of minor GI complaints. Individual patients, however, may find one formulation preferable to the other.

Five hundred and fifty-three patients received EC-NAPROSYN during long-term open label trials (mean length of treatment was 159 days) The rates for clinically-diagnosed peptic ulcers and GI bleeds were similar to what has been historically reported for long-term NSAID use.

INDIVIDUALIZATION OF DOSAGE

Although NAPROSYN, NAPROSYN Suspension, EC-NAPROSYN, ANAPROX and ANAPROX DS all circulate in the plasma as naproxen, they have pharmacokinetic differences that may affect onset of action. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium and within 1 hour in patients taking naproxen. Because EC-NAPROSYN dissolves in the small intestine rather than in the stomach, the absorption of the drug is delayed compared to the other naproxen formulations (see CLINICAL PHARMACOLOGY).

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events. A lower dose should be considered in patients with renal or hepatic im-

Analgesia/Dysmenorrhea/Bursitis and Tendonitis: Because the sodium salt of naproxen is more rapidly absorbed, ANAPROX/ANAPROX DS is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. The recommended starting dose is 550 mg

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tack has subsided. ANAPROX may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours as needed EC-NAPROSYN is not recommended because of the delay in absorption (see CLINICAL PHARMACOLOGY).

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis: The recommended dose of naproxen is NAPROSYN or NAPROSYN Suspension 250 mg, 375 mg or 500 mg taken twice daily (morning and evening) or EC-NAPROSYN 375 mg or 500 mg taken twice daily. Naproxen sodium may also be used (see DOSAGE AND ADMINISTRATION).

During long-term administration the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. In patients who tolerate lower doses well, the dose may be increased to 1500 mg per day when a higher level of anti-inflammatory/analgesic activity is required. When treating patients with naproxen 1500 mg/day (as NAPROSYN or 1650 mg of ANAPROX), the physician should observe sufficient increased clinical benefit to offset the potential increased risk. The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response (see CLINICAL PHARMACOLOGY).

Juvenile Arthritis: The use of NAPROSYN Suspension allows for more flexible dose titration. In pediatric patients, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen (see CLINICAL PHARMACOLOGY).

The recommended total daily dose is approximately 10 mg/kg given in two divided doses (ie, 5 mg/kg given twice a day) (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension are indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis.

Naproxen as NAPROSYN Suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the patient's weight

Naproxen as NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension are also indicated for the treatment of tendinitis, bursitis, acute gout, and for the management of pain and primary dysmenorrhea. EC-NAPROSYN is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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 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 naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (eg, aspirin hypersensitivity 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

gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if

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ulation 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 shown 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: **NAPROXEN-CONTAINING PRODUCTS SUCH AS NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS, NAPROSYN SUSPENSION, ALEVE®*, AND OTHER NAPROXEN PRODUCTS SHOULD NOT BE USED CONCOMITANTLY SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.**

If the steroid dose is reduced or eliminated during therapy the steroid dosage should be reduced slowly and the patients should 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.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing the utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory 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.

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, 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 nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and 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.

Naproxen and its metabolites are eliminated primarily by the kidneys; therefore, the drug should be used with 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 less than 20 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

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.

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.

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,

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 naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen 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 (eg, eosinophilia, rash, etc.), naproxen should be discontinued.

Fluid Retention and Edema: Peripheral edema has been observed in some patients receiving naproxen. Since each ANAPROX or ANAPROX DS tablet contains 25 mg or 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), and each teaspoonful of NAPROSYN Suspension contains 39 mg (about 1 5 mEq per each 125 mg of naproxen) of sodium, this should be considered in patients whose overall intake of sodium must be severely restricted For these reasons, ANAPROX, ANAPROX DS and NAPROSYN Suspension should be used with caution in patients with fluid retention, hypertension or heart failure.

Information for Patients: Naproxen, in NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension, like other drugs of this class, is not free of side effects. The side effects of these formulations of naproxen 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 that are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of naproxen treatment, particularly when it is 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 naproxen.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with naproxen for 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 (see WARNINGS: *Risk of GI Ulcerations, 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 sites other drugs that 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 (see CLINICAL STUDIES: *General Information*).

Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

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 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 naproxen is administered concomitantly with methotrexate Naproxen, naproxen sodium and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

Due to the gastric pH elevating effects of H2-blockers, sucralfate and intensive antacid therapy, concomitant administration of EC-NAPROSYN is not recommended.

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-corti-

NAPROSYN	250 mg	twice daily
	or 375 mg	twice daily
	or 500 mg	twice daily
ANAPROX	275 mg (naproxen 250 mg with 25 mg sodium)	twice daily
ANAPROX DS	550 mg (naproxen 500 mg with 50 mg sodium)	twice daily
NAPROSYN Suspension	250 mg (10 mL/2 tsp)	twice daily
	or 375 mg (15 mL/3 tsp)	twice daily
	or 500 mg (20 mL/4 tsp)	twice daily
EC-NAPROSYN	375 mg	twice daily
	or 500 mg	twice daily

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-hydroxy indoleacetic acid (5HIAA).

Carcinogenesis: A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16 and 24 mg/kg/day (50, 100 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, naproxen should not be used during pregnancy unless clearly needed.

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 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 plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use: Safety and effectiveness in pediatric patients 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 to 5 mg/kg (as naproxen suspension, see DOSAGE AND ADMINISTRATION), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

ADVERSE REACTIONS

The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between naproxen and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least 1 case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are treated below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see CLINICAL PHARMACOLOGY).

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

The following adverse reactions are divided into three parts based on frequency and causal relationship. Incidence greater than 1% (Probable Causal Relationship):

Gastrointestinal: 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 dis-

Cardiovascular: edema*, dyspnea*, palpitations

General: thirst

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

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. Those reactions observed through voluntary reporting since marketing are italicized.

Gastrointestinal: *abnormal liver function tests, colitis,* gastrointestinal bleeding and/or *perforation, hematemesis,* jaundice, pancreatitis, melena, 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, muscle weakness*

Dermatologic: *alopecia, photosensitive dermatitis, urticaria,* skin rashes, *photosensitivity reactions resembling porphyria cutanea tarda, epidermolysis bullosa*

Special Senses: *hearing impairment*

Cardiovascular: *congestive heart failure*

Respiratory: *eosinophilic pneumonitis*

General: *anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)*

Incidence less than 1% (Causal Relationship Unknown):

These observations are being listed to serve as alerting information to the physician.

Hematologic: *aplastic anemia, hemolytic anemia*

Central Nervous System: *aseptic meningitis, cognitive dysfunction*

Dermatologic: *epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome*

Gastrointestinal: *nonpeptic gastrointestinal ulceration, ulcerative stomatitis*

Cardiovascular: *vasculitis*

General: *hyperglycemia, hypoglycemia*

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 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

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

[See table above]

To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be broken, crushed or chewed during ingestion.

During long-term administration, the dose of naproxen 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 naproxen 1500 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see CLINICAL PHARMACOLOGY and INDIVIDUALIZATION OF DOSAGE)

Juvenile Arthritis: The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (ie, 5 mg/kg given twice a day) A measuring cup marked in $^1/_2$ teaspoon and 2 5 milliliter increments is provided with the NAPROSYN Suspension. The following table may be used as a guide for dosing of NAPROSYN Suspension.

EC-Naprosyn/Anaprox—Cont.

Patient's Weight	Dose	Administered as
13 kg (29 lb)	62.5 mg bid	2.5 mL (1/2 tsp) twice daily
25 kg (55 lb)	125 mg bid	5.0 mL (1 tsp) twice daily
38 kg (84 lb)	187 5 mg bid	7 5 mL (1 1/2 tsp) twice daily

Management of Pain, Primary Dysmenorrhea and Acute Tendonitis and Bursitis: The recommended starting dose is 550 mg of naproxen sodium as ANAPROX/ANAPROX DS followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. NAPROSYN may also be used but EC-NAPROSYN is not recommended for initial treatment of acute pain because absorption of naproxen is delayed compared to other naproxen-containing products (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE and INDIVIDUALIZATION OF DOSAGE)

Acute Gout: The recommended starting dose is 750 mg of NAPROSYN followed by 250 mg every 8 hours until the attack has subsided. ANAPROX may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours. EC-NAPROSYN is not recommended because of the delay in absorption (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

NAPROSYN Tablets: 250 mg: round, yellow, biconvex, debossed with ROCHE on one side and NAPROSYN 250 on the other Packaged in light-resistant bottles of 100 and 500.
100's (bottle): NDC 0004-6312-01; 500's (bottle): NDC 0004-6312-14.
375 mg: peach, capsule-shaped, debossed with NAPROSYN on one side and 375 on the other. Packaged in light-resistant bottles of 100 and 500.
100's (bottle). NDC 0004-6311-01; 500's (bottle). NDC 0004-6311-14.
500 mg: yellow, capsule-shaped, debossed with NAPROSYN on one side and 500 on the other. Packaged in light-resistant bottles of 100 and 500.
100's (bottle): NDC 0004-6310-01; 500's (bottle): NDC 0004-6310-14
Store at 15° to 30°C (59° to 86°F) in well-closed containers, dispense in light-resistant containers.
NAPROSYN Suspension: 125 mg/5mL (contains 39 mg sodium, about 1.5 mEq/teaspoon) Available in 1 pint (473 mL) light-resistant bottles (NDC 0004-0028-28).
Store at 15° to 30°C (59° to 86°F), avoid excessive heat, above 40°C (104°F). Dispense in light-resistant containers.
EC-NAPROSYN Delayed-Release Tablets: 375 mg: white, capsule-shaped, imprinted with EC-NAPROSYN on one side and 375 on the other Packaged in light-resistant bottles of 100.
100's (bottle). NDC 0004-6415-01.
500 mg: white, capsule-shaped, imprinted with EC-NAPROSYN on one side and 500 on the other. Packaged in light-resistant bottles of 100.
100's (bottle). NDC 0004-6416-01.
Store at 15° to 30°C (59° to 86°F) in well-closed containers, dispense in light-resistant containers.
ANAPROX Tablets: Naproxen sodium 275 mg blue, biconvex oval-shaped, debossed with ROCHE on one side and 274 on the other. Packaged in bottles of 100.
100's (bottle): NDC 0004-6201-01.
Store at 15° to 30°C (59° to 86°F) in well-closed containers.
ANAPROX DS Tablets: Naproxen sodium 550 mg: dark blue, capsule-shaped, film-coated, debossed with ROCHE on one side and ANAPROX DS on the other Packaged in bottles of 100 and 500.
100's (bottle): NDC 0004-6200-01; 500's (bottle): NDC 0004-6200-14.
Store at 15° to 30°C (59° to 86°F) in well-closed containers.
ALEVE is a registered trademark of Bayer-Roche L.L.C.
Naprosyn Suspension manufactured by Patheon Inc., Mississauga, Ontario, Canada L5N 7K9
Naprosyn Tablets, EC-Naprosyn Delayed-Release Tablets, Anaprox Tablets and Anaprox DS Tablets manufactured by Syntex Puerto Rico, Inc., Humacao, PR 00791
for:
Roche Pharmaceuticals
Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Revised: October 1998

Shown in Product Identification Guide, page 334

FORTOVASE™ Rx
(saquinavir)
SOFT GELATIN CAPSULES

The following text is complete prescribing information based on official labeling in effect June 1999.

DESCRIPTION

FORTOVASE brand of saquinavir is an inhibitor of the human immunodeficiency virus (HIV) protease FORTOVASE is available as beige, opaque, soft gelatin capsules for oral medium chain mono- and diglycerides, povidone and dl-alpha tocopherol. Each capsule shell contains gelatin and glycerol 85% with the following colorants: red iron oxide, yellow iron oxide and titanium dioxide. The chemical name for saquinavir is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[*N*-(2-quinolylcarbonyl)-*L*-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide which has a molecular formula $C_{38}H_{50}N_6O_5$ and a molecular weight of 670.86.
Saquinavir is a white to off-white powder and is insoluble in aqueous medium at 25°C.

MICROBIOLOGY

Mechanism of Action Saquinavir is an inhibitor of HIV protease. HIV protease is an enzyme required for the proteolytic cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Saquinavir is a peptide-like substrate analogue that binds to the protease active site and inhibits the activity of the enzyme. Saquinavir inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature noninfectious virus particles
Antiviral Activity In Vitro. In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic cell lines and in peripheral blood lymphocytes Saquinavir inhibited HIV activity in both acutely and chronically infected cells. IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were in the range of 1 to 30 nM and 5 to 80 nM, respectively; however, these concentrations may be altered in the presence of human plasma due to protein binding of saquinavir In cell culture saquinavir demonstrated additive to synergistic effects against HIV in double- and triple-combination regimens with reverse transcriptase inhibitors zidovudine, zalcitabine, didanosine, lamivudine, stavudine and nevirapine, without enhanced cytotoxicity. The relationship between in vitro susceptibility of HIV to saquinavir and inhibition of HIV replication in humans has not been established.
Drug Resistance: HIV isolates with reduced susceptibility to saquinavir (4-fold or greater increase in IC_{50} from baseline; ie, phenotypic resistance) have been selected in vitro. Genotypic analyses of these HIV isolates showed several mutations in the HIV-protease gene but only those at codons 48 (Gly→Val) and/or 90 (Leu→Met) were consistently associated with saquinavir resistance.
Isolates from selected patients with loss of antiviral activity and prolonged (range: 24 to 147 weeks) therapy with INVIRASE® (saquinavir mesylate) (alone or in combination with nucleoside analogues) showed reduced susceptibility to saquinavir Genotypic analysis of these isolates showed that mutations at amino acid positions 48 and/or 90 of the HIV-protease gene were most consistently associated with saquinavir resistance Other mutations in the protease gene were also observed. Mutations at codons 48 and 90 have not been detected in isolates from protease inhibitor naive patients.
In a study (NV15107) of treatment-experienced patients receiving FORTOVASE monotherapy (1200 mg tid) for 8 weeks followed by antiretroviral combination therapy for a period of 4 to 48 weeks (median 32 weeks), 10 of 32 patients showed genotypic changes associated with reduced susceptibility to saquinavir. However, for resistance evaluation virus could not be recovered from 11 of 32 patients
In a study (NV15355) of treatment-naive patients receiving FORTOVASE in combination with two nucleoside analogues for a period of 16 weeks, 1 of 28 patient isolates showed genotypic changes at codon 71 and 90 in the HIV-protease gene.
Cross-resistance. Among protease inhibitors variable cross-resistance has been recognized. Analysis of saquinavir-resistant isolates from patients following prolonged (24 to 147 weeks) therapy with INVIRASE showed that a majority of patients had resistance to at least one of four other protease inhibitors (indinavir, nelfinavir, ritonavir, 141W94).

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetic properties of saquinavir when administered as FORTOVASE have been evaluated in healthy volunteers (n=207) and HIV-infected patients (n=91) after single-oral doses (range: 300 mg to 1200 mg) and multiple-oral doses (range: 400 mg to 1200 mg tid). The disposition properties of saquinavir have been studied in healthy volunteers after intravenous doses of 6, 12, 36 or 72 mg (n=21).
ABSORPTION AND BIOAVAILABILITY IN ADULTS: Following multiple dosing of FORTOVASE (1200 mg tid) in HIV-infected patients in study NV15107, the mean steady-state area under the plasma concentration versus time curve (AUC) at week 3 was 7249 ng·h/mL (n=31) compared to 866 ng·h/mL (n=10) following multiple dosing with 600 mg tid of INVIRASE (Table 1) Preliminary results from a pharmacokinetic substudy of NV15182 showed a mean saquinavir AUC of 3485 (CV 66%) ng·h/mL (n=11) in patients sampled between weeks 61 to 69 of therapy (see PRECAUTIONS: *General*) While this mean AUC value was lower than that of the week 3 steady-state value for FORTOVASE (1200 mg tid) from study NV15107, it re-

Table 1. Mean AUC_8 in Patients Treated With FORTOVASE and INVIRASE (Week 3)

Treatment	n	AUC_8 ng·h/mL	± SD
FORTOVASE 1200 mg tid	31	7249	± 6174
INVIRASE 600 mg tid	10	866	± 533

The absolute bioavailability of saquinavir administered as FORTOVASE has not been assessed. However, following single 600-mg doses, the relative bioavailability of saquinavir as FORTOVASE compared to saquinavir administered as INVIRASE was estimated as 331% (95% CI 207% to 530%) The absolute bioavailability of saquinavir administered as INVIRASE average 4% (CV 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600-mg dose of INVIRASE following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat, 1006 kcal). In healthy volunteers receiving single doses of FORTOVASE (300 mg to 1200 mg) and in HIV-infected patients receiving multiple doses of FORTOVASE (400 mg to 1200 mg tid), a greater than dose-proportional increase in saquinavir plasma concentrations has been observed
Comparison of pharmacokinetic parameters between single- and multiple-dose studies shows that following multiple dosing of FORTOVASE (1200 mg tid) in healthy male volunteers (n=18), the steady-state AUC was 80% (95% CI 22% to 176%) higher than that observed after a single 1200-mg dose (n=30).
HIV-infected patients administered FORTOVASE (1200 mg tid) had AUC and maximum plasma concentration (C_{max}) values approximately twice those observed in healthy volunteers receiving the same treatment regimen The mean AUC values at week 1 were 4159 (CV 88%) and 8839 (CV 82%) ng·h/mL, and C_{max} values were 1420 (CV 81%) and 2477 (CV 76%) ng/mL for healthy volunteers and HIV-infected patients, respectively.
FOOD EFFECT: The mean 12-hour AUC after a single 800-mg oral dose of saquinavir in healthy volunteers (n=12) was increased from 167 ng·h/mL (CV 45%), under fasting conditions, to 1120 ng·h/mL (CV 54%) when FORTOVASE was given with breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal).
DISTRIBUTION IN ADULTS: The mean steady-state volume of distribution following intravenous administration of a 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions into tissues. It has been shown that saquinavir, up to 30 µg/mL is approximately 97% bound to plasma proteins.
METABOLISM AND ELIMINATION IN ADULTS: In vitro studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on in vitro studies, saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir mesylate (n=8), 88% and 1% of the orally administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg ^{14}C-saquinavir intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In mass balance studies, 13% of circulating radioactivity in plasma was attributed to unchanged drug after oral administration and the remainder attributed to saquinavir metabolites. Following intravenous administration, 66% of circulating radioactivity was attributed to unchanged drug and the remainder attributed to saquinavir metabolites, suggesting that saquinavir undergoes extensive first-pass metabolism.
Systemic clearance of saquinavir was rapid, 1.14 L/h/kg (CV 12%) after intravenous doses of 6, 36 and 72 mg. The mean residence time of saquinavir was 7 hours (n=8).
SPECIAL POPULATIONS: Hepatic or Renal Impairment: Saquinavir pharmacokinetics in patients with hepatic or renal insufficiency has not been investigated (see PRECAUTIONS). Only 1% of saquinavir is excreted in the urine, so the impact of renal impairment on saquinavir elimination should be minimal.
Gender, Race and Age: The effect of gender was investigated in healthy volunteers receiving single 1200-mg doses of FORTOVASE (n=12 females, 18 males) No effect of gender was apparent on the pharmacokinetics of saquinavir in this study.
The effect of race on the pharmacokinetics of saquinavir when administered as FORTOVASE is unknown.
The pharmacokinetics of saquinavir when administered as FORTOVASE has not been investigated in patients >65 years of age or in pediatric patients (<16 years of age)
DRUG INTERACTIONS (see PRECAUTIONS: *Drug Interactions*) Several drug interaction studies have been completed with both INVIRASE and FORTOVASE. Results from studies conducted with INVIRASE may not be applicable to FORTOVASE Table 2 summarizes the effect of FORTOVASE on the geometric mean AUC and C_{max} of coadministered drugs. Table 3 summarizes the effect of coadmin-