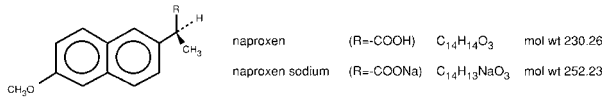
EC-NAPROSYN® (naproxen delayed-release tablets)
NAPROSYN® (naproxen tablets)
ANAPROX®/ANAPROX®DS (naproxen sodium tablets)
NAPROSYN®(naproxen suspension)

R_x only

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 and naproxen sodium have the following structures, respectively:



Naproxen has a molecular weight of 230.26 and a molecular formula of $C_{14}H_{14}O_3$. Naproxen sodium has a molecular weight of 252.23 and a molecular formula of $C_{14}H_{13}NaO_3$.

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) is available as yellow tablets containing 250 mg of naproxen, peach tablets containing 375 mg of naproxen and yellow tablets containing 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, iron oxides, povidone and magnesium stearate.

EC-NAPROSYN (naproxen delayed-release tablets) is available as enteric-coated white tablets containing 375 mg of naproxen and 500 mg of naproxen for oral administration. The inactive ingredients are 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.

ANAPROX (naproxen sodium tablets) is available as blue tablets containing 275 mg of naproxen sodium and ANAPROX DS (naproxen sodium tablets) is available as dark blue tablets containing 550 mg of naproxen sodium for oral administration. The inactive ingredients are 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) is available as a light orange-colored opaque oral suspension containing 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

Pharmacodynamics: 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 mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

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 with the observed differences in pattern of absorption, the 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:

	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%)
$AUC_{0–12\ hr}$ (µg·hr/mL)	845 (20%)	767 (15%)

*Mean value (coefficient of variation)

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). The naproxen anion has been found in the milk of lactating women at a concentrations equivalent to approximately 1% of maximum naproxen concentration in plasma (see PRECAUTIONS: *Nursing Mothers*).

Metabolism:

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

Excretion:

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 (see PRECAUTIONS: *Renal Effects*).

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.

Geriatric Patients: Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is less than 1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

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. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine < 30 ml/min) (see PRECAUTIONS: *Renal Effects*).

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, 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.

In a clinical trial comparing standard formulations of naproxen 375 mg bid (750 mg a day) vs 750 mg bid (1500 mg/day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen 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 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 (e.g., 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.

Geriatric Patients: The hepatic and renal tolerability of long-term naproxen administration was studied in two double blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. Naproxen was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

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 impairment or in elderly patients (see PRECAUTIONS).

Analgesia/Dysmenorrhea/Bursitis and Tendinitis: 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 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 for treatment of acute pain and dysmenorrhea. 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 and INDICATIONS AND USAGE).

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 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 for up to 6 months 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 is indicated:

- For the relief of the signs and symptoms of rheumatoid arthritis
- For the relief of the signs and symptoms of osteoarthritis
- For the relief of the signs and symptoms of ankylosing spondylitis

- For the relief of the signs and symptoms of 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 is also indicated:

- For relief of the signs and symptoms of tendinitis
- For relief of the signs and symptoms of bursitis
- For relief of the signs and symptoms of acute gout
- For the management of pain
- For the management of 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 (see WARNINGS: *Anaphylactoid Reactions* and PRECAUTIONS: *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation: Serious gastrointestinal toxicity such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms (see PRECAUTIONS: *Hematological Effects*). Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur.

The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, 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. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to naproxen. Naproxen should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS: *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease: In cases with advanced kidney disease, treatment with naproxen is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS: *Renal Effects*).

Pregnancy: In late pregnancy, as with other NSAIDs, naproxen should be avoided because it may cause premature closure of the ductus arteriosus.

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.**

Naproxen cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient 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 g 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 their 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.

Hepatic Effects: 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 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 (e.g., eosinophilia, rash, etc.), naproxen should be discontinued.

Renal Effects: Caution should be used when initiating treatment with naproxen in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with naproxen. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS: *Advanced Renal Disease*).

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 impaired renal function, renal failure, acute interstitial nephritis, hematuria, proteinuria, renal papillary necrosis, 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, caution should be observed since administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation or failure. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, 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 such patients and the monitoring of serum creatinine and/or creatinine clearance is advised. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine < 30 ml/min).

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.

Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs, including naproxen. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including naproxen, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Naproxen does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving naproxen who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

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.

Preexisting Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, naproxen should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients: Naproxen, in NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS: *Gastrointestinal (GI) Effects-Risk of GI Ulceration, Bleeding, and Perforation*).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (eg, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy, naproxen, in NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS, and NAPROSYN SUSPENSION, should be avoided because it may cause premature closure of the ductus arteriosus.

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 ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, naproxen should be discontinued.

Drug Interactions:

Aspirin: 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.

Methotrexate: 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.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (see PRECAUTIONS: *Renal Effects).*

Furosemide: Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Lithium: Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that patients taking both drugs have a risk of serious GI bleeding that is higher than patients taking either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

Other Information Concerning Drug Interactions:

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

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.

Due to the gastric pH elevating effects of H_2-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-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-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 C. 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.

Labor and Delivery: In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

Nursing Mothers: The naproxen anion has been found in the milk of lactating women at a concentrations equivalent to approximately 1% of maximum naproxen concentration 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.

Geriatric Use: 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.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. While age does not appear to be an independent risk factor for the development of peptic ulceration and bleeding with naproxen administration, elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population (see WARNINGS).

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs (see PRECAUTIONS: *Renal Effects*).

ADVERSE REACTIONS

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

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1 to 10% of patients are:

Gastrointestinal (GI) Experiences, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, vertigo

Dermatologic: pruritus (itching) *, skin eruptions*, ecchymoses*, sweating, purpura

Special Senses: tinnitus*, visual disturbances, hearing disturbances

Cardiovascular: edema*, palpitations

General: dyspnea*, thirst

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

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1 to 10% of patients.

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through post-marketing reports. Those adverse reactions observed through post-marketing reports are italicized.

Body as a Whole: *anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)*

Cardiovascular: *congestive heart failure, vasculitis*

Gastrointestinal: gastrointestinal bleeding and/or *perforation, hematemesis,* jaundice, pancreatitis, vomiting, *colitis, abnormal liver function tests, nonpeptic gastrointestinal ulceration, ulcerative stomatitis*

Hemic and Lymphatic: *eosinophilia, leucopenia,* melena, thrombocytopenia, agranulocytosis, *granulocytopenia, hemolytic anemia, aplastic anemia*

Metabolic and Nutritional: *hyperglycemia, hypoglycemia*

Nervous System: inability to concentrate, *depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction*

Respiratory: *eosinophilic pneumonitis*

Dermatologic: *alopecia, urticaria,* skin rashes, *toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.*

Special Senses: *hearing impairment*

Urogenital: *glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis*

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death

Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, hepatitis, eructation, liver failure

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis

Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

OVERDOSAGE

Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, 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.

Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis:

NAPROSYN	250 mg or 375 mg or 500 mg	twice daily twice daily 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) or 375 mg (15 mL/3 tsp) or 500 mg (20 mL/4 tsp)	twice daily twice daily twice daily
EC-NAPROSYN	375 mg or 500 mg	twice daily twice daily

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 of up to 6 months 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).

Geriatric Patients: 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.

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:

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, engraved with NPR LE 250 on one side and scored on the other. Packaged in light-resistant bottles of 100.

100's (bottle): NDC 0004-6313-01.

375 mg: pink, biconvex oval, engraved with NPR LE 375 on one side. Packaged in light-resistant bottles of 100 and 500.

100's (bottle): NDC 0004-6314-01; 500's (bottle): NDC 0004-6314-14.

500 mg: yellow, capsule-shaped, engraved with NPR LE 500 on one side and scored on the other. Packaged in light-resistant bottles of 100 and 500.

100's (bottle): NDC 0004-6316-01; 500's (bottle): NDC 0004-6316-14.

Store at 15° to 30°C (59° to 86°F) in well-closed containers; dispense in light-resistant containers.

NAPROSYN Suspension: 125 mg/5 mL (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: light blue, oval-shaped, engraved with NPS-275 on one side. Packaged in bottles of 100.

100's (bottle): NDC 0004-6202-01.

Store at 15° to 30°C (59° to 86°F) in well-closed containers.

ANAPROX DS Tablets: Naproxen sodium 550 mg: dark blue, oblong-shaped, engraved with NPS 550 on one side and scored on both sides. Packaged in bottles of 100 and 500.

100's (bottle): NDC 0004-6203-01; 500's (bottle): NDC 0004-6203-14.

Store at 15° to 30°C (59° to 86°F) in well-closed containers.

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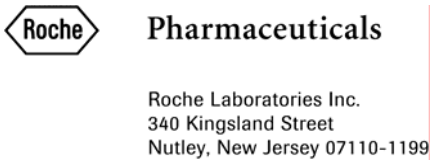

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