PRODUCT MONOGRAPH

[Pr]APO-NAPROXEN

Naproxen Tablets

125 mg, 250 mg, 375 mg and 500 mg

USP

[Pr]APO-NAPROXEN SR

Naproxen Sustained-Release Tablets

750 mg

Apotex Standard

[Pr]APO-NAPROXEN EC

Naproxen Enteric-Coated Tablets

250 mg, 375 mg and 500 mg

Apotex Standard

Non-Steroidal Anti-Inflammatory Drug (NSAID)

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Control No# 168736

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[Pr]APO-NAPROXEN
Naproxen Tablets

[Pr]APO-NAPROXEN SR
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[Pr]APO-NAPROXEN EC
Naproxen Enteric-Coated Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	APO-NAPROXEN: Tablets;125 mg, 250 mg, 375 mg and 500 mg APO-NAPROXEN SR: Sustained-Release Tablets; 750 mg APO-NAPROXEN EC: Enteric-Coated Tablets; 250 mg, 375 mg and 500 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APO-NAPROXEN (naproxen) is indicated for:

- The treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

- The relief of minor aches and pains in muscles, bones and joints, mild to moderate pain accompanied by inflammation in musculoskeletal injuries (sprains and strains) and primary dysmenorrhea.

Modified release formulations of naproxen (i.e., APO-NAPROXEN EC and APO-NAPROXEN SR) are not recommended for initial treatment of acute pain because the absorption of naproxen is delayed.

For patients with an increased risk of developing cardiovascular and/or gastrointestinal adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of APO-NAPROXEN should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

APO-NAPROXEN, as a NSAID, does NOT treat clinical disease or prevent its progression.

APO-NAPROXEN, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (> 65 years of age):

Evidence from clinical studies and post-market experience suggests that use in the geriatric population is associated with differences in safety (see WARNINGS AND PRECAUTIONS).

Pediatrics (< 18 years of age):

APO-NAPROXEN is contraindicated in children and adolescents less than 18 years of age. (see CONTRAINDICATIONS).

CONTRAINDICATIONS

APO-NAPROXEN (naproxen) is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although APO-NAPROXEN has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.

- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition

- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants

- severe uncontrolled heart failure

- known hypersensitivity to naproxen or to any of the components/excipients

- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance-rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions, Anaphylactoid Reactions).

- active gastric / duodenal / peptic ulcer, active GI bleeding.

- cerebrovascular bleeding or other bleeding disorders

- inflammatory bowel disease

- severe liver impairment or active liver disease

- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see WARNINGS AND PRECAUTIONS: Renal)

- known hyperkalemia (see WARNINGS AND PRECAUTIONS: Renal, Fluid and Electrolyte Balance)

- children and adolescents less than 18 years of age since APO-NAPROXEN has not been studied in subjects under the age of 18.

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (See WARNINGS AND PRECAUTIONS - Cardiovascular).

APO-NAPROXEN is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing APO-NAPROXEN to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as APO-NAPROXEN, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. (see also WARNINGS AND PRECAUTIONS: Renal, Fluid and Electrolyte Balance)

Randomized clinical trials with APO-NAPROXEN have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing APO-NAPROXEN.

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS: Gastrointestinal).

Use of NSAIDs, such as APO-NAPROXEN, is associated with an increased incidence of gastrointestinal adverse events (such as ulceration, bleeding, perforation and obstruction of the upper and lower gastrointestinal tract).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

APO-NAPROXEN is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See DRUG INTERACTIONS: Drug-Drug Interactions, Acetylsalicylic acid (ASA) or other NSAIDs)

APO-NAPROXEN (naproxen) should not be used concomitantly with the related drug APO-NAPRO-NA (naproxen sodium) since they both circulate in plasma as the naproxen anion.

Carcinogenesis and Mutagenesis

There is no evidence from animal data that naproxen is carcinogenic or mutagenic (see Part II, TOXICOLOGY, for animal studies).

Cardiovascular and Cerebrovascular Events

APO-NAPROXEN is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing APO-NAPROXEN to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list)

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as APO-NAPROXEN, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing APO-NAPROXEN should hypertension either develop or worsen with its use.

Use of NSAIDs, such as APO-NAPROXEN, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See WARNINGS AND PRECAUTIONS: Renal, Fluid and Electrolyte Balance).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Endocrine and Metabolism

Corticosteroids: APO-NAPROXEN (naproxen) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. (see DRUG INTERACTIONS: Drug-Drug Interactions, Glucocorticoids)

Gastrointestinal

Serious GI toxicity (sometimes fatal), such as ulceration, inflammation gastrointestinal bleeding, perforation and obstruction of the upper and lower gastrointestinal tract, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as APO-NAPROXEN (naproxen). Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with APO-NAPROXEN, even in the absence of previous GI tract symptoms.

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. (see WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics)

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using APO-NAPROXEN and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing APO-NAPROXEN to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10- fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID.

Should urinary symptoms occur, in the absence of an alternate explanation, treatment with APO-NAPROXEN should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed when APO-NAPROXEN is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of bleeding. Concurrent therapy of APO-NAPROXEN with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

***Anti-platelet Effects*:** NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

APO-NAPROXEN and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (see DRUG INTERACTIONS: Drug-Drug Interactions, Acetylsalicylic Acid or other NSAIDs)

Concomitant administration of APO-NAPROXEN with low dose ASA increases the risk of GI ulceration and associated complications.

***Blood dyscrasias*:** Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

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

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown, but caution is advised when high doses are required. It is prudent to use the lowest effective dose.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Hypersensitivity Reactions:

***Anaphylactoid Reactions*:** As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to naproxen. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving naproxen. APO-NAPROXEN should NOT be given to patients with the ASA-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 ASA or other NSAIDs (see CONTRAINDICATIONS).

***ASA-Intolerance*:** APO-NAPROXEN should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see CONTRAINDICATIONS).

Cross-sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions: (See WARNINGS AND PRECAUTIONS: Skin)

Immune

(See WARNINGS AND PRECAUTIONS: Infection, Aseptic Meningitis)

Infection
APO-NAPROXEN, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis*:* Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic
Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as APO-NAPROXEN. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop, APO-NAPROXEN should be discontinued and an ophthalmologic examination performed.
Ophthalmologic examination should be carried out at periodic intervals in any patient receiving APO-NAPROXEN for an extended period of time.

Peri-Operative Considerations
(See CONTRAINDICATIONS: Coronary Artery Bypass Graft Surgery)

Psychiatric
(See WARNINGS AND PRECAUTIONS: Neurologic)

Renal
Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.
Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, cyclosporin, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs.

Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as APO-NAPROXEN, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

Advanced Renal Disease*:* (See CONTRAINDICATIONS)

Fluid and Electrolyte Balance: Use of NSAIDs, such as APO-NAPROXEN, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing APO-NAPROXEN in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see WARNINGS AND PRECAUTIONS: Cardiovascular). Use of NSAIDs, such as APO-NAPROXEN, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics. Electrolytes should be monitored periodically (see CONTRAINDICATIONS).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function/Reproduction

The use of APO-NAPROXEN, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of APO-NAPROXEN should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations

Pregnant Women: **APO-NAPROXEN is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see TOXICOLOGY).**

Caution should be exercised in prescribing APO-NAPROXEN during the first and second trimesters of pregnancy (see TOXICOLOGY).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

APO-NAPROXEN is not recommended in labour and delivery because, through their prostaglandin synthesis inhibitory effect, they may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

Nursing Women: (See CONTRAINDICATIONS)

Pediatrics: **(**See CONTRAINDICATIONS**)**

Geriatrics: Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests

Patients on long-term treatment with APO-NAPROXEN should have their blood pressure monitored regularly and an ophthalmic examination should be carried out at periodic intervals (See WARNINGS AND PRECAUTIONS: Cardiovascular and Ophthalmic).

Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should

be checked in patients on long-term treatment with APO-NAPROXEN. Additionally, concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR) (See WARNINGS AND PRECAUTIONS: Hematology).

Serum transaminase and bilirubin should be monitored regularly during APO-NAPROXEN therapy (see WARNINGS AND PRECAUTIONS: Hepatic, Biliary, Pancreatic).

Serum creatinine, creatine clearance and serum urea should be checked in patient during APO-NAPROXEN therapy. Electrolytes including serum potassium should be monitored periodically (see WARNINGS AND PRECAUTIONS: Renal).

Monitoring of plasma lithium concentration is recommended when stopping or starting APO-NAPROXEN therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions encountered with non-steroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred particularly in the elderly.

As with all drugs in this class, the frequency and severity of adverse events depends on several factors: the dose of the drug and duration of treatment; the age, the sex, physical condition of the patient; any concurrent medical diagnoses or individual risk factors.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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.

The adverse reactions in controlled clinical trials in 960 patients with rheumatoid arthritis or osteoarthritis treated with the naproxen standard tablets are listed below.

Table 1: Most Common Clinical Trial Adverse Drug Reactions (3%-9% and 1%-3%)

Body System	Incidence	Adverse Reaction
Gastrointestinal	3%-9%	Heartburn, constipation, abdominal pain, nausea
	1%-3%	Diarrhea, dyspepsia, stomatitis, diverticulitis, gastrointestinal bleeding

Body System	Incidence	Adverse Reaction
Central Nervous System	3%-9%	Headache, dizziness, drowsiness
	1%-3%	Light-headedness, vertigo, depression, fatigue. Occasionally patients had to discontinue treatment because of the severity of some of these complaints (headache and dizziness).
Dermatologic	3%-9%	Pruritus, ecchymoses, skin eruptions
	1%-3%	Sweating, purpura
Cardiovascular	3%-9%	Dyspnea, peripheral edema
	1%-3%	Palpitations
Special Senses	3%-9%	Tinnitus
	1%-3%	Hearing disturbances
General	1%-3%	Thirst

Table 2: Less Common Clinical Trial Adverse Drug Reactions (<1%)

Gastrointestinal	gastrointestinal bleeding, hematemesis, melena, peptic ulceration with or without bleeding and/or perforation, vomiting, ulcerative stomatitis.
Central Nervous System	inability to concentrate, malaise, myalgia, insomnia and cognitive dysfunction (i.e. decreased attention span, loss of short-term memory, difficulty with calculations).
Dermatologic	alopecia, urticaria, skin rash, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, photosensitive dermatitis, exfoliative dermatitis, erythema nodosum.
Hepatic	Abnormal liver function tests, jaundice, cholestasis and hepatitis.
Cardiovascular	congestive heart failure and vasculitis.
Renal	Glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, nephropathy and tubular necrosis.
Hematologic	Eosinophilia, granulocytopenia, leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia and hemolytic anemia.

Special Senses	hearing impairment and visual disturbances.
Reproductive, female	infertility
General	muscle weakness, anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever), angioneurotic edema, hyperglycemia, hypoglycemia and eosinophilic pneumonitis.

Post-Market Adverse Drug Reactions

The following additional adverse events have been reported with NSAIDs including naproxen and naproxen sodium:

Gastrointestinal	Inflammation, bleeding (sometimes fatal, particularly in the elderly), ulceration, perforation and obstruction of the upper or lower gastrointestinal tract. Oesophagitis, gastritis, pancreatitis, stomatitis. Exacerbation of ulcerative colitis and Crohn's disease. Heartburn, dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, flatulence, constipation, haematemesis, melaena.
Infections	aseptic meningitis
Blood and Lymphatic System Disorders	agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia, leucopoenia, thrombocytopenia
Immune System	anaphylactoid reactions
Disorders	
Metabolic and Nutrition Disorders	hyperkalemia
Psychiatric Disorders:	depression, dream abnormalities, insomnia
Nervous System	dizziness, drowsiness, headache, lightheadedness, retrobulbar optic neuritis convulsions, cognitive dysfunction, inability to concentrate
Eye Disorders:	visual disturbances, corneal opacity, papillitis, papilloedema
Ear and Labyrinth Disorders:	hearing impairment, hearing disturbances, tinnitus, vertigo
Cardiac Disorders:	palpitations, cardiac failure has been reported in association with NSAID treatment, congestive heart failure
Vascular	hypertension, vasculitis

Disorders:	Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Respiratory, Thoracic and Mediastinal Disorders:	dyspnoea, pulmonary oedema, asthma, eosinophilic pneumonitis.
Hepatobiliary Disorders:	hepatitis (some cases of hepatitis have been fatal), jaundice.
Skin and Subcutaneous Tissue Disorders:	ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, alopecia, epidermal necrolysis, very rarely toxic epidermal necrolysis, erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, SLE, urticaria, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda ("pseudoporphyria") or epidermolysis bullosa and angioneurotic oedema. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.
Musculoskeletal and Connective Tissue Disorders:	myalgia, muscle weakness.
Renal and Urinary Disorders:	haematuria, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis
Reproductive System and Breast Disorders:	female infertility
General Disorders and Administration Site Conditions:	oedema, thirst, pyrexia (chills and fever), malaise
Investigations:	abnormal liver function tests, raised serum creatinine

DRUG INTERACTIONS

Drug-Drug Interactions

Acetylsalicylic acid (ASA) or other NSAIDs: The use of APO-NAPROXEN (naproxen) in addition to any other NSAID, including over -the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.
Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Albumin Bound Drugs: The naproxen anion may displace from their binding sites other drugs which are also albumin–bound and may lead to drug interactions. For example, in patients receiving bishydroxycoumarin or warfarin, the addition of APO-NAPROXEN could prolong the prothrombin time. These patients should, therefore, be under careful observation. Similarly, patients receiving APO-NAPROXEN and a hydantoin, sulfonamide, or sulfonylurea should be observed for adjustment of dose if required.

Antacids: The rate of absorption of naproxen is altered by concomitant administration of antacids but is not adversely influenced by the presence of food.

Anti-coagulants: (See WARNINGS AND PRECAUTIONS: Hematologic, Anticoagulants)

Anti-hypertensives: NSAIDs may diminish the anti-hypertensive effect of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Concomitant use of NSAIDs with ACE inhibitors or angiotensin receptor blockers may increase the risk of renal dysfunction, especially in patients with pre-existing poor renal function (see WARNINGS AND PRECAUTIONS: Renal).

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers as well as other antihypertensive agents.

Anti-platelet Agents (including ASA): There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as APO-NAPROXEN. (see WARNINGS AND PRECAUTIONS: Hematologic, Anti-platelet Effects).

***Cyclosporin**:* Inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporine and/or the risk of cyclosporine induced nephrotoxicity. Patients should be carefully monitored during concurrent use.

***Cholestyramine*:** Concomitant administration of cholestyramine can delay the absorption of naproxen, but does not affect its extent.

Digoxin: Concomitant administration of an NSAID with digoxin can result in an increase in digoxin concentrations which may result in digitalis toxicity. Increased monitoring and dosage adjustments of digitalis glycosides may be necessary during and following concurrent NSAID therapy.

Diuretics: Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.

***Glucocorticoids**:* Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

***Lithium**:* Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.

***Methotrexate**:* Caution is advised in the concomitant administration of naproxen and methotrexate since naproxen and other non-steroidal anti-inflammatory agents have been reported to reduce the tubular secretion of methotrexate in an animal model, thereby possibly enhancing its toxicity.

Probenecid: Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half–life significantly. Caution is advised when probenecid is administered concurrently.

Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see WARNINGS AND PRECAUTIONS: Gastrointestinal).

Drug-Food Interactions

Concomitant administration of food can delay the absorption of naproxen, but does not affect its extent.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

There are no specific studies about effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances or other central nervous system disturbances should refrain from these activities.

Concurrent use of alcohol with an NSAID may increase the risk of gastrointestinal side effects, including ulceration and hemorrhage.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adult:

Use of APO-NAPROXEN should be limited to the lowest effective dose for the shortest possible duration of treatment (see INDICATIONS AND CLINICAL USE). For all indications, treatment must be initiated with the lowest dose.

Osteoarthritis / Rheumatoid Arthritis / Ankylosing Spondylitis

Oral: The usual total dosage of naproxen for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis is 250 mg twice a day. It may be increased gradually to 375 mg or 500 mg twice a day, depending on the patient's response.

Recommended Daily Dosing		
APO-NAPROXEN (Tablets)	125 mg or 250 mg or 375 mg or 500 mg	twice daily twice daily twice daily twice daily
APO-NAPROXEN EC (Enteric Coated Tablets)	250 mg or 375 mg or 500 mg	twice daily twice daily twice daily
APO-NAPROXEN SR (Sustained Release Tablets)	750 mg	once daily

Studies have not shown any clinically significant benefit in using doses higher than 1000 mg/day. In patients who tolerate lower doses of naproxen well and who exhibit only a partial response to 1000 mg/day, the dose may be increased to 1500 mg/day for limited periods. Experience with 1500 mg/day naproxen is limited to using the standard tablets. APO-NAPROXEN (naproxen) tablets should be swallowed with food or milk.

When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk (see ADVERSE REACTIONS).

In addition, patients on 1500 mg/day need to be followed closely for the development of any adverse events.

During long–term administration, the dose of APO-NAPROXEN may be adjusted up or down depending on the clinical response of the patient. A lower dose may suffice for long–term administration.

Patients with rheumatoid arthritis or osteoarthritis maintained on a dose of 750 mg/day or 1000 mg/day in divided doses can be switched to a once daily dose of APO-NAPROXEN SR (naproxen sustained-release) 750 mg respectively. The single daily dose of APO-NAPROXEN SR should not be exceeded and can be administered in the morning or evening. APO-NAPROXEN SR tablets should be swallowed whole.

APO-NAPROXEN SR (naproxen sustained-release) tablets and APO-NAPROXEN EC (naproxen enteric-coated) tablets have not been studied in subjects under the age of 18.

Analgesia / Musculoskeletal Injuries

Oral: The recommended dose for naproxen is 750 mg/day divided into either two or three doses/day. This may be increased to 500 mg twice a day if needed. The lowest effective dose should be used.

Modified release formulations of naproxen (i.e. enteric-coated and sustained-release) are not recommended for initial treatment of acute pain because the absorption of naproxen is delayed.

Dysmenorrhea

Oral: The recommended starting dose for naproxen is two 250 mg tablets (or one 500 mg tablet), followed by one 250 mg tablet every 6 – 8 hours, as required. The total daily dose should not exceed 5 tablets (1250 mg). Alternatively, one 500 mg tablet given twice daily may be used.

Modified release formulations of naproxen (i.e. enteric-coated and sustained-release) are not recommended for initial treatment of acute pain because the absorption of naproxen is delayed.

Missed Dose
The missed dose should be taken as soon as remembered, and then the regular dosing schedule should be continued. Two doses of APO-NAPROXEN should not be taken at the same time.

Administration
APO-NAPROXEN SR and APO-NAPROXEN EC tablets should be swallowed whole.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms and Signs

Significant overdosage may be characterized by drowsiness, dizziness, disorientation, heartburn, indigestion, epigastric pain, abdominal discomfort, nausea, vomiting, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis and apnea. A few patients have experienced convulsions, but it is not clear whether or not these were naproxen related.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.

Anaphylactoid reactions have been repeated with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Treatment

Patients should be managed by symptomatic and supportive care following NSAIDs overdose. There are no specific antidotes. Prevention of further absorption (e.g. activated charcoal) may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

APO-NAPROXEN contains naproxen, a member of the arylacetic acid group of NSAIDs.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic properties. The mechanism of action of naproxen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacodynamics
(See DETAILED PHARMACOLOGY)

Pharmacokinetics
Naproxen is rapidly and completely absorbed from the gastro-intestinal tract. After oral administration of naproxen, peak plasma levels of naproxen anion are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4 to5 doses. Plasma naproxen levels and areas under plasma concentration vs. time curves increased linearly with dose increments up to 500 mg twice a day, but larger doses resulted in a plateau effect. The mean biological half-life of the anion in humans is approximately 13 hours, and at therapeutic levels it is greater than 99% albumin bound. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-0-desmethyl naproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes.

When naproxen is administered in the sustained-release form, the peak plasma levels are delayed and the maximum plasma concentrations are reduced compared to those seen with standard release formulations of naproxen. The minimum plasma concentrations, at steady state, are equivalent between naproxen (sustained-release tablet) given once a day and the corresponding standard dosage given twice a day. The peak to trough plasma concentration ratio of 2.2 and 2.6 observed with the standard tablet formulation (375 mg twice daily and 500 mg twice daily respectively) is reduced to 1.6 and 1.8 with the 750 and 1000 mg naproxen (sustained-release tablets) respectively, resulting in smaller fluctuations in plasma concentrations of naproxen with the sustained-release naproxen tablets.

The average T_{max} of naproxen in subjects receiving the 1000 mg sustained-release tablet immediately after a high-fat meal did not differ significantly when compared to the fasting state (7.7 hours post-prandial; 9.7 hours fasting). The average C_{max} increased significantly from 63.1 μg/mL (fasting) to 86.1 μg/mL (post-prandial). This increase in C_{max} was still lower than that observed with the 1000 mg dose of naproxen (standard) tablets. Based upon the 95% confidence interval, the AUCs were equivalent when the naproxen (sustained-release) tablet was administered under fasting and non-fasting conditions.

A 28-day study of chromium-51-labeled red blood cell loss in feces was conducted with the 750 mg sustained-release naproxen tablets in 20 patients. There was no statistically significant difference in red blood cell loss between patients 60 years of age or younger and those over 60. Enteric-coated naproxen is designed to be dispersed and dissolved in the small bowel rather than the stomach, so the absorption is delayed until the stomach is emptied. Naproxen (enteric-coated tablets) were bioequivalent to the standard 375 mg and 500 mg tablets, except for a substantially increased time to peak plasma concentration (T_{max}). The average maximum plasma concentration (C_{max}) following the 375 mg, 2 x 250 mg and 500 mg enteric-coated tablets were 47.9, 58.2 and 60.7 μg/mL, while the C_{max} following the 375 mg and 500 mg standard

immediate release tablets were 46.6 and 63.1 µg/mL respectively. The T_{max}'s were 4.5, 4.2 and 4.2 hours for the respective enteric-coated formulations, as compared to 2.3 and 2.6 hours after standard naproxen tablets. At steady state (multiple dosing) naproxen (enteric-coated) and naproxen (standard) were equivalent to each other with respect to C_{max}, C_{ave}, C_{max}/C_{ave}, 0-12 hours AUC and half-life. In addition, fluctuations in plasma levels about C_{ave} were considerably less with naproxen (enteric-coated) tablets as compared to standard naproxen (49.3% vs. 85.3%). Administration of 500 mg enteric-coated naproxen tablets with food and antacid did not alter the extent of absorption of naproxen as compared to the fasting condition. However, antacid treatment resulted in a higher C_{max} (70.7 vs. 58.5 µg/mL) and earlier T_{max} (5.2 hours vs. 8.7 hours) in comparison to the fasting condition. Relative to the fasting state, the average T_{max} was delayed following a high fat meal (5.6 – 8.7 hours fasting, 9.2 – 10.8 hours post prandial) while the average C_{max} and AUC were bioequivalent.

STORAGE AND STABILITY

Store at room temperature 15-30°C (59-86°F).

Keep out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-NAPROXEN is available as:

APO-NAPROXEN Tablets:

APO-NAPROXEN 125 mg tablets: Each pale green, oval, biconvex tablet engraved "APO-125" on one side, contains 125 mg naproxen. Available in bottles of 100 and 500 tablets.

APO-NAPROXEN 250 mg tablets: Each yellow, oval, biconvex tablet engraved "APO-250" on one side contains 250 mg naproxen. Available in bottles of 100 and 1000 tablets.

APO-NAPROXEN 375 mg tablets: Each peach-coloured, capsule-shaped, biconvex tablet, scored and engraved "APO 375" on one side, contains 375 mg naproxen. Available in bottles of 100 and 500 tablets.

APO-NAPROXEN 500 mg tablets: Each yellow, capsule-shaped, biconvex tablet, scored and engraved "APO 500" on one side, contains 500 mg naproxen. Available in bottles of 100 and 500 tablets.

Sustained-Release Tablets:

APO-NAPROXEN SR 750 mg tablets: Each peach, capsule-shaped, biconvex tablet, engraved “APO-750” on one side, contains 750 mg of naproxen. Available in bottles of 100 and 500 and unit dose packages of 100 (10x10).

Enteric-Coated Tablets:

APO-NAPROXEN EC 250 mg tablets: Each white, round, biconvex, enteric-coated tablet, engraved “APO” on one side, and “250” on the other side, contains 250 mg of naproxen. Available in bottles of 100 and 500 and unit dose packages of 60 (6 x 10).
APO-NAPROXEN EC 375 mg tablets: Each white, capsule-shaped, biconvex, enteric-coated tablet, engraved “APO” on one side, and “375” on the other side, contains 375 mg of naproxen. Available in bottles of 100 and 500 and unit dose packages of 60 (6 x 10).
APO-NAPROXEN EC 500 mg tablets: Each white, capsule-shaped, biconvex, enteric-coated tablet, engraved “APO” on one side, and “500” on the other side contains 500 mg of naproxen. Available in bottles of 100 and 500 and unit dose packages of 30 (3 x 10).

APO- NAPROXEN Tablets contain the following non-medicinal ingredients: methylcellulose , croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide. The 250 and the 500 mg tablets also contain D&C yellow #10 and FD&C yellow #6; the 375 mg tablets contain only the latter; the 125 mg tablets contain the former and FD&C blue #2.

APO-NAPROXEN SR Tablets contain the following non-medicinal ingredients hydroxypropyl methylcellulose, FD&C yellow #6, D&C yellow #10, and magnesium stearate.

APO-NAPROXEN EC Tablets contain the following non-medicinal ingredients methylcellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, hydroxyethyl cellulose, polyethylene glycol, titanium dioxide, triethyl citrate, talc and methacrylic acid copolymer.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

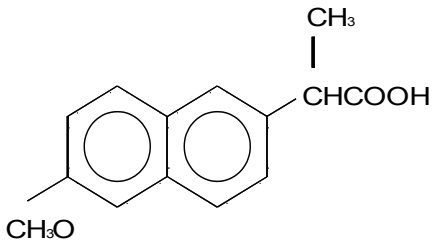
Drug Substance

Proper/Common Name: Naproxen

Chemical Name: (+)-6-methoxy-alpha-methyl-2-naphthalene acetic acid

Molecular formula and molecular mass: $C_{14}H_{14}O_3$; 230.27g/mol

Structural Formula:



Physicochemical properties: Naproxen is an odourless white crystalline powder with a melting point of 152° - 158°C. It is highly lipid soluble, sparingly soluble in water at low pH, and highly soluble in water at high pH.

CLINICAL TRIALS

Comparative Bioavailability

A randomized, single dose, blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on male volunteers. The results obtained from 16 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of naproxen was measured and compared following a single oral dose (2 x 250 mg tablets) of Apo-Naproxen (naproxen) 250 mg tablet (Apotex Inc.) and Naprosyn (naproxen) 250 mg tablet (Syntex, Inc.).

Naproxen (2 x 250 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)#	90% Confidence Interval (%)#
AUC_{0-32} (mcg•h/mL)	907.2 912.6 (11.2)	926.0 931.0 (10.6)	98.0	95.5 – 100.5
AUC_{0-inf} (mcg•h/mL)	1108.5 1120.2 (15.0)	1135.9 1145.9 (13.8)	97.6	94.8 – 100.4
Cmax (mcg/mL)	73.5 73.8 (10.0)	73.1 73.4 (10.4)	100.6	96.5 – 104.8
Tmax§ (h)	2.1 (62.5)	2.1 (41.6)		
t½ § (h)	14.2 (11.4)	14.3 (9.5)		

* Apo–Naproxen (naproxen) 250 mg tablets (Apotex Inc.)

† Naprosyn (naproxen) 250 mg tablets (Syntex, Inc.) was purchased in Canada.

Based on Least Squares Means.

§ Expressed as arithmetic means (CV%) only.

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 14 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of naproxen was measured and compared following a single oral dose (1 x 750 mg tablets) of Apo-Naproxen SR (naproxen) 750 mg tablet (Apotex Inc.) and Naprosyn SR (naproxen) 750 mg tablet (Syntex, Inc.).

Naproxen (1 x 750 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)#	90% Confidence Interval (%)#
AUC_{0-T} (mcg•h/mL)	1339 1366 (18)	1326 1336 (14)	101	93 - 110
AUC_{0-24} (mcg•h/mL)	685 696 (19)	721 732 (18)	95	89 – 103
AUC_{0-inf} (mcg•h/mL)	1466 1494 (18)	1480 1488 (13)	99	94 - 106
C_{max} (mcg/mL)	39.3 39.9 (18)	41.7 42.7 (24)	94	88 - 100
Tmax§ (h)	15.1 (60)	11.2 (75)		
Half-life § (h)	16.7 (14)	16.8 (15)		

* Apo–Naproxen SR (naproxen) 750 mg tablets (Apotex Inc.)

† Naprosyn SR (naproxen) 750 mg tablets (Syntex, Inc.) was purchased in Canada.

Based on Least Squares Means.

§ Expressed as arithmetic means (CV%) only.

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy male volunteers. The results obtained from 16 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of naproxen was measured and compared following a single oral dose (1 x 750 mg tablets) of Apo-Naproxen SR (naproxen) 750 mg tablet (Apotex Inc.) and Naprosyn SR (naproxen) 750 mg tablet (Syntex, Inc.).

Naproxen (1 x 750 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)#	90% Confidence Interval (%)#
AUC_{0-T} (mcg•h/mL)	1495 1524 (21)	1422 1449 (20)	105	101 – 109
AUC_{0-24} (mcg•h/mL)	1012 1021 (13)	992 998 (12)	102	99 – 105
AUC_{0-inf} (mcg•h/mL)	1604 1642 (21)	1541 1570 (20)	104	100 – 109
C_{max} (mcg/mL)	74.4 75.3 (16)	78.3 79.3 (14)	95	90 - 99
Tmax§ (h)	5.81 (20)	5.69 (19)		
Half-life § (h)	15.0 (19)	14.8 (21)		

* Apo–Naproxen SR (naproxen) 750 mg tablets (Apotex Inc.)

† Naprosyn SR (naproxen) 750 mg tablets (Syntex, Inc.) was purchased in Canada.

Based on Least Squares Means.

§ Expressed as arithmetic means (CV%) only.

A multiple dose, 2-way crossover comparative bioavailability study, conducted at steady state, was performed on healthy male volunteers. The results obtained from 14 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of naproxen was measured and compared following multiple oral doses (1 x 750 mg tablet administered once daily for 7 days) of Apo-Naproxen SR (naproxen) 750 mg tablet (Apotex Inc.) and Naprosyn SR (naproxen) 750 mg tablet (Syntex, Inc.).

Naproxen (1 x 750 mg once daily for 7 days) From Measured Data Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means (%)[#]	90% Confidence Interval (%)[#]
AUC_{SS} (mcg•h/mL)	1163 1181 (18)	1195 1210 (16)	97	88 – 108
C_{max} (mcg/mL)	67.5 69.0 (22)	70.2 70.9 (14)	96	86 – 107
C_{min} (mcg/mL)	32.6 33.8 (27)	32.8 33.5 (20)	99	87 - 114
Tmax[§] (h)	4.21 (19)	4.21 (36)		

* Apo–Naproxen SR (naproxen) 750 mg tablets (Apotex Inc.)

[†] Naprosyn SR (naproxen) 750 mg tablets (Syntex, Inc.) was purchased in Canada.

[#] Based on Least Squares Means.

[§] Expressed as arithmetic means (CV%) only.

Two additional comparative bioavailability studies were performed using enteric-coated tablets, under fed and fasting conditions. The rate and extent of absorption of naproxen was measured and compared following oral administration of a single 1 x 500 mg dose of Apo-Naproxen EC (naproxen) enteric-coated tablets, or Naprosyn ® E (naproxen) enteric-coated tablets. The results from measured data are summarized below.

Summary Table of the Comparative Bioavailability Data Naproxen EC (Dose: 1 x 500 mg) From Measured Data - Under Fasting Conditions Based on Naproxen				
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
Parameter	Apo-Naproxen EC	Naprosyn® E †		
AUC_T (:g.h/mL)	1133 1141 (12)	1047 1071 (19)	108.2	98.5 – 118.8
AUC_I (:g.h/mL)	1203 1215 (14)	1114 1143 (21)	108.0	98.4 – 118.6
C_{MAX} (:g/mL)	61.6 62.6 (18)	60.0 62.5 (27)	102.6	91.8 – 114.7
T_{MAX}^{*} (h)	5.75 (49)	5.97 (72)		
$T_{½}^{*}$ (h)	17.1 (12)	17.3 (16)		
Arithmetic means (CV%). * Based on the least squares estimate. Naprosyn® E is marketed by Hoffmann-La Roche Limited (Mississauga, Ontario, Canada).				

Summary Table of the Comparative Bioavailability Data Naproxen EC (Dose: 1 x 500 mg) From Measured Data - Under Fed Conditions Based on Naproxen				
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
Parameter	Apo-Naproxen EC	Naprosyn® E †		
AUC_T (:g.h/mL)	1053 1088 (25)	1100 1123 (21)	96.6	87.8 – 106.2
AUC_I (:g.h/mL)	1158 1208 (29)	1219 1260 (27)	96.0	87.5 – 105.3

Summary Table of the Comparative Bioavailability Data Naproxen EC (Dose: 1 x 500 mg) From Measured Data - Under Fed Conditions Based on Naproxen				
C_{MAX} (:g/mL)	59.3 60.6 (21)	61.7 62.7 (17)	96.3	85.0 – 109.1
T_{MAX}^{*} (h)	16.1 (38)	14.3 (51)		
$T_{½}^{*}$ (h)	17.0 (18)	17.6 (19)		
Arithmetic means (CV%). * Based on the least squares estimate. Naprosyn® E is marketed by Hoffmann-La Roche Limited (Mississauga, Ontario, Canada).				

DETAILED PHARMACOLOGY

Naproxen has been shown to possess anti-inflammatory and analgesic activity as assessed by a variety of animal test procedures.

Anti-inflammatory activity: In the rat paw edema assay, naproxen was more potent than phenylbutazone and acetylsalicylic acid, and slightly less potent than indomethacin.

In the rat granuloma assay, naproxen was more active than phenylbutazone, and less active than indomethacin.

Analgesic activity: In a mouse analgesic assay using phenylquinone for pain induction, naproxen was more active than phenylbutazone and acetylsalicylic acid, and less active than indomethacin. Parallel comparative analgesic studies were done in rats with yeast-induced paw edema.

In these assays, naproxen had a higher relative potency than phenylbutazone and acetylsalicylic acid, but lower relative potency when compared to indomethacin.

The comparative absorption, distribution, metabolism, and excretion of naproxen were studied in several species, including man. Naproxen was found to be rapidly absorbed in all species and, once in the blood, was eliminated with half-lives ranging from 2 to 35 hours. Estimated volumes of distribution indicated that a large fraction of the drug is held in the blood, much like salicylates are. Virtually all of the drug present in the blood of humans was determined to be unchanged naproxen, while the rat and the monkey showed minor amounts of transformation products. With the exception of the dog, all species excreted naproxen and its metabolic transformation products predominantly in the urine. In the dog, the preferred route was fecal.

Studies by Tomlinson *et al* have shown that naproxen can inhibit the synthesis of prostaglandin E_2 from arachidonic acid by bovine seminal vesicle microsomes. Naproxen therefore appears to act, at least in part, in a manner similar to other anti-inflammatory agents which block prostaglandin biosynthesis.

Human metabolic studies:

The plasma-level response to oral naproxen doses ranging up to 900 mg twice daily was studied in normal subjects. Experiments with tritium-labelled naproxen showed that there was no difference in the fraction of ingested drug excreted in the stools whether the dose was 250 mg or 900 mg, thus eliminating the possibility that this effect was a result of incomplete absorption. Accelerated renal clearance at high doses because of disproportionate increases in the amount of unbound drug appeared to be the most likely explanation for the plateau effect.

In patients treated with maintenance dialysis for terminal renal failure, serum level studies indicated that the metabolite 6-0-desmethyl naproxen is dialysed, whilst naproxen is not. No accumulation of naproxen was found although serum levels of the metabolite increased.

TOXICOLOGY

Acute Animal Toxicity

The oral LD_{50} values for naproxen are as follows:

Hamsters:	4110 mg/kg
Rats:	543 mg/kg
Dogs:	> 1000 mg/kg
Mice:	1234 mg/kg

Subacute and Chronic Oral Toxicity

In subacute and chronic oral studies with naproxen in a variety of species, the principal pathologic effect was gastrointestinal irritation and ulceration. The lesions seen were predominantly in the small intestine and ranged from hyperemia to perforation and peritonitis.

Nephropathy was seen occasionally in rats, mice, and rabbits at high-dose levels of naproxen, but not in rhesus monkeys or miniature pigs. In the affected species, the pathologic changes occurred in the cortex and papilla. Some rats examined 14 days after single oral doses of 230 mg/kg or more of naproxen evidenced necrotic areas of cortical and papillary tissue. Tubular dilation (ectasia) occurred in rabbits dosed orally for 14 days with 200 mg/kg/day or more of naproxen. An examination of unfixed renal tissue from rabbits so treated was conducted and revealed the presence of diffraction patterns similar to that of crystalline naproxen. This suggests that the ectasia observed was a physical response to deposition of excreted naproxen within the tubules.

In mice given oral doses of 120 mg/kg/day or more of naproxen for 6 months, the kidneys were characterized by a low, but non-dosage-related incidence of cortical sclerosis and papillary tip necrosis. Chronic administration of high doses of naproxen to mice appears to be associated with exacerbation of spontaneous murine nephropathy.

A wide variation in susceptibility to gastrointestinal lesions from administration of naproxen was evident in the various species tested. For example, 30 mg/kg/day was tolerated well by rats for 90 days, but the same dose was ulcerogenic when administered for 6 months. Rhesus monkeys and miniature swine exhibited no significant pathology when dosed with naproxen at 45 mg/kg/day for 30 days. This dose of naproxen was also tolerated by miniature swine without obvious evidence of adverse effects when administered daily for one year. In rhesus monkeys, doses as high as 120 mg/kg/day administered twice daily for 6 months produced no clinical or histopathological evidence of gastrointestinal irritation although occult blood in the feces occurred more frequently in these animals as compared to controls. In rabbits, the maximum tolerated repeated oral dose is 200 mg/kg/day. Mice tolerated oral daily doses of 240 mg/kg/day for 6 months. In both rabbits and mice, gastrointestinal and renal toxicity was reported at these dose levels. In dogs, on the other hand, 5.0 mg/kg/day approaches the maximum tolerated dose. This peculiar canine susceptibility to gastrointestinal effects of non-steroidal anti-inflammatory agents has also been shown with indomethacin and ibuprofen.

In dogs, naproxen exhibits a considerably longer plasma half-life than it does in rats, guinea pigs, miniature swine, monkeys and man. The same observation has been made with ibuprofen in dogs compared to rats and man. In addition, in the species listed, only the dog excretes significant amounts of administered naproxen in the feces (50%). In the rat, guinea pigs, miniature swine, monkeys, and man, 86-94% of the administered drug is excreted in the urine. The suggested enterohepatic circulation of naproxen in the dog (as judged by the fecal excretion) may be a major factor in the susceptibility of the dog to gastrointestinal irritation by this compound.

Pathologic changes in the spleen and mesenteric lymph nodes as well as peritoneal inflammation and adhesions were considered to be clearly secondary to the effects of high doses of naproxen on the gastrointestinal tract. Moderate weight loss of the male secondary sex glands occurred in some studies in naproxen-treated rats and dogs. Histopathologically, the affected glands in some instances exhibited atrophic and/or hypoplastic changes characterized by decreased secretory material. A possible estrogenic action of naproxen as a causative factor seems highly unlikely since in standard bioassay procedures, the drug exhibited no estrogenic activity.

Nevertheless, daily doses of naproxen as high as 30 mg/kg administered for 60 days before mating had no effect on fertility and reproductive performance of male rats. These results reflect the physiological integrity of the entire male reproductive apparatus after administration of naproxen throughout the spermatogenic cycle.

Effect on Induced Infections in Rabbits

To determine whether treatment with naproxen affects the ability of animals to respond to bacterial infection, rabbits were inoculated subcutaneously with *Diplococcus pneumoniae*. For 21 days before bacterial challenge and during a 2-week post-challenge period, the animals were dosed daily by gavage with 2, 10, or 20 mg/kg of naproxen. Clinical conditions, morbidity, mortality, gross and histopathologic changes were evaluated. There were no apparent effects of naproxen in altering the response of the animals to bacterial challenge.

Teratology

In teratology studies, no skeletal or visceral anomalies or pathologic changes were induced in the fetuses of pregnant rats and rabbits treated during organogenesis with daily oral doses of naproxen up to 20 mg/kg. In these studies, there were also no significant differences from controls in the number of live fetuses, resorptions, fetal weights or ano-genital distances.

Reproductive Studies

Daily oral administration of 15, 30 or 60 mg/kg of naproxen to female rabbits from 2 weeks before mating until day 20 of pregnancy did not affect fertility, gestation, or the numbers of live fetuses.

In a peri- and post-natal study in rats, oral doses of naproxen up to 20 mg/kg administered daily during the last part of pregnancy through weaning did not result in adverse effects in viability of pups, lactation index, sex ratio, or weight gain of offspring. However, there was a slight increase in gestation length at the 10 and 20 mg/kg dose levels; and at the 10 mg/kg dose level, there was a significant increase in stillbirths.

Naproxen at daily oral doses of 12, 36 or 108 mg/kg to female mice from 2 weeks before mating until weaning of the pups did not cause changes in length of gestation, number of live pups born, average pup weight at 0, 4, 7, 14 or 21 days, or sex distribution. The fertility index, gestation index, and 4-day viability index were similar for mice from the control and treated groups. The 21-day survival and lactation indexes were decreased for mice from the group fed 108 mg/kg/day of naproxen, but not for mice given 12 or 36 mg/kg/day. Most of this change was due to maternal mortality in the high dose group.

Recent evidence suggests that inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory compounds may be related to decreased uterine contractibility. Thus, the onset of labor in a rat model system can be delayed with naproxen administration without causing maternal or fetal deaths in excess of that seen in controls. Since it has been shown that naproxen inhibits prostaglandin synthesis in vitro, it has been suggested that the effects of naproxen on uterine contractility are mediated through that mechanism.

Maternal and fetal deaths seen in naproxen-treated rats were, therefore, apparently related to dystocia rather than to a direct toxic effect of the compound. Naproxen is not unique in this regard, since comparable results were obtained in the rat with other commonly used non-steroidal anti-inflammatory agents.

Carcinogenicity

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24 mg/kg/day. Naproxen was not carcinogenic in rats.

Mutagenicity

Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines), *Sachharomyces cerevisisae* (1 cell line), and mouse lymphoma tests.