PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-NAPROXEN

Naproxen Tablets

Tablets, 125 mg, 250 mg, 375 mg and 500 mg, Oral

USP

PrAPO-NAPROXEN SR

Naproxen Sustained-Release Tablets

Sustained-Release Tablets, 750 mg, Oral

Apotex Standard

PrAPO-NAPROXEN EC

Naproxen Enteric-Coated Tablets

Enteric-Coated Tablets, 250 mg, 375 mg and 500 mg, Oral

Apotex Standard

ATC Code: M01AE02

Non-Steroidal Anti-Inflammatory Drug (NSAID)

APOTEX INC.
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Toronto, Ontario
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Date of Initial Authorization:
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July 26, 2023

Submission Control Number: 272842

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	07/2023
3 SERIOUS WARNING AND PRECAUTIONS BOX	07/2023
7 WARNINGS AND PRECAUTIONS	07/2023
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	07/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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., enteric coated and sustained release) 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 2 CONTRAINDICATIONS and 7 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 2 CONTRAINDICATIONS and 7 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.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of naproxen in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 4 DOSAGE AND ADMINISTRATION and 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

APO-NAPROXEN is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although 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
- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING
- 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 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance, 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 7 WARNINGS AND PRECAUTIONS, Renal
- known hyperkalemia. See 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance
- children and adolescents less than 18 years of age since naproxen has not been studied in subjects under the age of 18.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV):**

  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.

  Randomized clinical trials with naproxen have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing APO-NAPROXEN. See 7 WARNINGS AND PRECAUTIONS

- **Risk of Gastrointestinal (GI) Adverse Events:**

  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). See 7 WARNINGS AND PRECAUTIONS: Gastrointestinal

- **Risk in Pregnancy:**

  Caution should be exercised in prescribing APO-NAPROXEN during the first and second trimesters of pregnancy. Use of APO-NAPROXEN at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see 7.1.1 Pregnant Women). APO-NAPROXEN is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition). See 2 CONTRAINDICATIONS

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Use of APO-NAPROXEN should be limited to the lowest effective dose for the shortest possible duration of treatment. See 1 INDICATIONS.**
- **For all indications, treatment must be initiated with the lowest dose. Other 250 mg naproxen formulations are available for the 250 mg tablet starting dose.**
- 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). See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX
- 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.
- A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients.

4.2 Recommended Dose and Dosage Adjustment

Adult:

Osteoarthritis / Rheumatoid Arthritis / Ankylosing Spondylitis

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.

When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk. See 8 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 or 1000 mg/day in divided doses can be switched to a once daily dose of APO-NAPROXEN SR 750 mg. The single daily dose of APO-NAPROXEN SR should not be exceeded and can be administered in the morning or evening.

Analgesia / Musculoskeletal Injuries

The recommended dose for naproxen is 250 mg three times a day or 375 mg twice a day. This may be increased to 500 mg twice a day if needed. The lowest effective dose should be used.

Dysmenorrhea

The recommended starting dose for naproxen is two 250 mg tablets (or one 500 mg tablet), followed by one 250 mg tablet every 6 to 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.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

Geriatrics (>65 years of age): In the elderly, frail and debilitated, the dosage should be reduced to the lowest level providing control of symptoms, and adjusted when necessary. See 7.1.4 Geriatrics

Renal impairment: A lower dose should be considered in patients with mild and moderate renal impairment. APO-NAPROXEN is contraindicated in 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 2 CONTRAINDICATIONS

Hepatic impairment: A lower dose should be considered in patients with mild and moderate hepatic impairment. APO-NAPROXEN is contraindicated in severe liver impairment or active liver disease. See 2 CONTRAINDICATIONS

4.4 Administration

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

4.5 Missed Dose

If a dose is missed, the patient should take it as soon as it is recognized. If it is almost time for the next dose, skip the missed dose and continue with the next scheduled dose. The patient should be instructed not take 2 doses at the same time.

5 OVERDOSAGE

Frequently observed signs and symptoms of overdose are 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.

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablets, 125 mg, 250 mg, 375 mg and 500 mg	Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and methylcellulose. The 250 and the 500 mg tablets also contain D&C yellow #10 and FD&C yellow #6; the 375 mg tablets contain only FD&C yellow #6; the 125 mg tablets contain D&C yellow #10 and FD&C blue #2.
	Sustained-Release Tablets, 750 mg	D&C yellow #10, FD&C yellow #6, hydroxypropyl methylcellulose and magnesium stearate.
	Enteric-coated Tablets, 250 mg, 375 mg and 500 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxyethyl cellulose, magnesium stearate, methacrylic acid copolymer, methylcellulose, polyethylene glycol, talc, titanium dioxide and triethyl citrate.

Description

APO-NAPROXEN is available as:

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 (10 x 10).
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).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 9.4 Drug-Drug Interactions, Acetylsalicylic acid (ASA) or other NSAIDs

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

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY

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 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.

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.**

Driving and Operating Machinery

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.

Endocrine and Metabolism

Corticosteroids: APO-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 9.4 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. 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 7.1.4 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 to 6 months, and in about 2 to 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. See 9 DRUG INTERACTIONS

***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 9.4 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 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.

Immune

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.

Monitoring and Laboratory Tests

Cardiovascular: 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.

Hematology: 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).

Hepatic: Serum transaminase and bilirubin should be monitored regularly during APO-NAPROXEN therapy.

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

Pregnancy: If APO-NAPROXEN is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on APO-NAPROXEN be closely monitored for amniotic fluid volume since APO-NAPROXEN may result in reduction of amniotic fluid volume and even oligohydramnios. See 7.1.1 Pregnant Women

APO-NAPROXEN is contraindicated for use in the third trimester of pregnancy.

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 2 CONTRAINDICATIONS

Psychiatric

Some patients may experience depression with the use of NSAIDs, such as naproxen.

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 2 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.

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 2 CONTRAINDICATIONS

Reproductive Health: Female and Male Potential

- **Fertility**

  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. See 7.1.1 Pregnant Women

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.

Sensitivity/Resistance

***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 2 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 2 CONTRAINDICATIONS

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

Skin

Serious skin reactions: Use of some NSAIDs, such as naproxen, have been associated with rare post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS)
- toxic epidermal necrolysis (TEN)
- exfoliative dermatitis
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

7.1 Special Populations

7.1.1 Pregnant Women

APO-NAPROXEN is contraindicated for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition. See 2 CONTRAINDICATIONS and 16 NON-CLINICALTOXICOLOGY. Caution is recommended in prescribing APO-NAPROXEN during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and postmarketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if APO-NAPROXEN treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or 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.

7.1.2 Breast-feeding

APO-NAPROXEN is contraindicated in breast-feeding women. See 2 CONTRAINDICATIONS

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of naproxen in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

7.1.4 Geriatrics

Geriatrics (> 65 years of age): 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. See 7 WARNINGS AND PRECAUTIONS

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2: Most Common Clinical Trial Adverse Drug Reactions (3% to 9% and 1% to 3%)

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

Body System	Incidence	Adverse Reaction
	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

8.3 Less Common Clinical Trial Adverse Reactions

Table 3: 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.

8.5 Post-Market Adverse Reactions

Additional reports of serious adverse events temporally associated with naproxen during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to naproxen exposure.

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 Disorders:	anaphylactoid reactions
Metabolic and Nutrition Disorders:	hyperkalemia
Psychiatric Disorders:	depression, dream abnormalities, insomnia
Nervous System Disorders:	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 Disorders:	hypertension, vasculitis 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

9 DRUG INTERACTIONS

9.3 Drug-Behavioural 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.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) or other NSAIDs	CT	• The concomitant use of APO-NAPROXEN and other NSAIDs (such as ASA and ibuprofen) does not produce any greater therapeutic effect than the use of NSAIDs alone. • The concomitant use of an NSAID and ASA (such as aspirin) was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. • Clinical PD data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose ASA on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. See 10.2 Pharmacodynamics	• Because there may be an increased risk of CV events following discontinuation of naproxen due to the interference with the antiplatelet effect of ASA during the washout period, for patients taking low-dose ASA for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of ASA, or non-NSAID analgesics where appropriate. • Concomitant use of APO-NAPROXEN and analgesic doses of ASA or other NSAIDs is not recommended because of the increased risk of bleeding. See 7 WARNINGS AND PRECAUTIONS

Proper/Common name	Source of Evidence	Effect	Clinical comment
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	T	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have RI, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure and hyperkalemia. These effects are usually reversible.	• 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. See 7 WARNINGS AND PRECAUTIONS, Renal
Albumin-Bound Drugs	T	• 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, warfarin, sulfonamide or sulphonylureas, hydantoins, other NSAIDs, and ASA.	• Patients should be under carful observation for adjustment of dose if required.
Antacids	N/A	• Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.	• Concomitant administration is not recommended.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Anti-coagulants	CT	• Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. • The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.	• Anticoagulation/INR should be monitored and warfarin dosage adjustments. See 7 WARNINGS AND PRECAUTIONS, Hematologic, Anticoagulants
Anti-platelets Agents (including ASA)	CT	• There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with naproxen.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-platelet Effects
Cyclosporin and Tacrolimus	T	• Inhibition of renal prostaglandin activity by NSAIDs may increase the nephrotoxic effect of cyclosporin or tacrolimus.	• Patients should be monitored for necessary dosage adjustment. • Monitor patients for signs of worsening renal function.
Cholestyramine	N/A	• Concomitant administration of cholestyramine can delay the absorption of naproxen.	• Concomitant administration is not recommended.
Digoxin	C	• The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin which may result in digitalis toxicity.	• Monitor serum digoxin levels.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Diuretics	CT	• Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. • This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.	• Observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. See 7 WARNINGS AND PRECAUTIONS
Glucocorticoids	CT	• The concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding, especially in older (>65 years of age) patients.	• Monitor patients particularly those over 65 years of age for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS
Lithium	CT	• NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.	• Monitor patients for plasma lithium concentrations when stopping or starting a NSAID.
Methotrexate	N/A	• Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).	• Monitor patients for methotrexate toxicity.
Pemetrexed	CT	• Concomitant use of APO-NAPROXEN and pemetrexed	• In patients with RI whose creatinine clearance ranges

Proper/Common name	Source of Evidence	Effect	Clinical comment
		may increase the risk of pemetrexed- associated myelosuppression, renal, and GI toxicity.	from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.
Probenecid	CT	• Increases naproxen anion plasma levels and extends its plasma half-life significantly.	• Patients should be observed for adjustment of dose if required.
Selective serotonin reuptake inhibitors (SSRIs)	C	• Serotonin release by platelets plays an important role in hemostasis. • Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal
Quinolone antibacterials	C	• There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.	• Patients should be observed for adjustment of dose if required.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; GI = Gastrointestinal; CV = Cardiovascular; INR = International normalized ratio; PD = Pharmacodynamic; ASA = Acetylsalicylic acid; NSAID = Non-Steroidal Anti-Inflammatory Drug; ACE = Angiotensin converting enzyme; ARB = Angiotensin Receptor Blockers; RI = Renal impairment;

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Bleeding times: Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

Porter-Silber test: The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Urinary assays of 5-hydroxy indoleacetic acid (5HIAA): Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA). This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid is determined.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

APO-NAPROXEN contains naproxen, a propionic acid derivative related to the arylacetic acid group of NSAIDs.

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

10.2 Pharmacodynamics

In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once daily with low-dose immediate release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 inhibition at 24 hours following the day 10 dose [98.7% (aspirin alone) vs 93.1% (naproxen and aspirin)]. The interaction was observed even following discontinuation of naproxen on day 11 (while aspirin dose was continued) but normalized by day 13. In the same study, the interaction was greater when naproxen was administered 30 minutes prior to aspirin [98.7% vs 87.7%] and minimal when aspirin was administered 30 minutes prior to naproxen [98.7% vs 95.4%].

Following administration of naproxen 220 mg twice-daily with low-dose immediate-release aspirin (first naproxen dose given 30 minutes prior to aspirin), the interaction was minimal at 24 h following day 10 dose [98.7% vs 95.7%]. However, the interaction was more prominent after discontinuation of naproxen (washout) on day 11 [98.7% vs 84.3%] and did

not normalize completely by day 13 [98.5% vs 90.7%]. See 9 DRUG INTERACTIONS

10.3 Pharmacokinetics

Absorption

Naproxen is rapidly and completely absorbed from the gastro-intestinal tract. After oral administration of naproxen (standard release), peak plasma levels of naproxen anion are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4 to 5 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.

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 mcg/mL, while the C_{max} following the 375 mg and 500 mg standard immediate release tablets were 46.6 and 63.1 mcg/mL, respectively. The $T_{max's}$ were 4.5, 4.2 and 4.2 hr. for the respective enteric-coated formulations as compared to 2.3 and 2.6 hr. 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 to 12 hr. AUC and half-life. In addition, fluctuation in plasma levels about C_{ave} were considerably less with naproxen (enteric coated) 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 mcg/mL) and earlier T_{max} (5.2 hr vs. 8.7 hr.) in comparison to the fasting condition. Relative to the fasting state, the average T_{max} was delayed following a high fat meal (5.6 to 8.7 hr. fasting, 9.2 to 10.8 hr. post-prandial) while the average C_{max} and AUC were bioequivalent.

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 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 mcg/mL (fasting) to 86.1 mcg/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.

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.

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. See 7.1.2 Breast-feeding

Metabolism

Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Elimination

The mean biological half-life of the anion in humans is approximately 13 hours.

The clearance of naproxen is 0.13 mL/min/kg. 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. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure, metabolites may accumulate.

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.

Special Populations and Conditions

Pediatrics: The pharmacokinetic profile of naproxen in children aged 5 to 16 years with arthritis is similar to that in adults although the clearance is generally higher in children than in adults. Pharmacokinetic studies of naproxen were not performed in children less

than 5 years of age. Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS.

Geriatric: 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 <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.

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

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.

Renal impairment: Given that naproxen and its metabolites are primarily excreted by the kidney, the potential exists for accumulation in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. See 2 CONTRAINDICATIONS.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

N/A

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

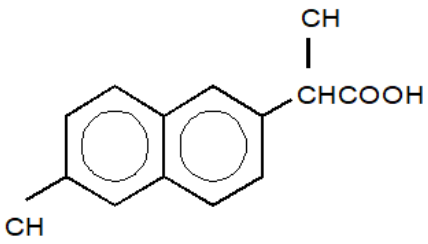
Drug Substance

Proper name: Naproxen

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

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

Structural formula:



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

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A randomized, single dose (2 x 250 mg), blinded, 2-way crossover comparative bioavailability study of APO-NAPROXEN (Apotex Inc.) and NAPROSYN (Syntex Inc.) was conducted in healthy male volunteers under fasting conditions. A summary of the comparative bioavailability data from 16 volunteers that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Naproxen (2 x 250 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% 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_I (mcg•h/mL)	1108.5 1120.2 (15.0)	1135.9 1145.9 (13.8)	97.6	94.8 – 100.4
C_{max} (mcg/mL)	73.5 73.8 (10.0)	73.1 73.4 (10.4)	100.6	96.5 – 104.8
T_{max}[3] (h)	2.1 (62.5)	2.1 (41.6)		
$T_{½}$[3] (h)	14.2 (11.4)	14.3 (9.5)		

[1] APO-NAPROXEN (naproxen) tablets, 250 mg (Apotex Inc.)
[2] NAPROSYN (naproxen) tablets, 250 mg (Syntex, Inc. Canada)
[3] Expressed as arithmetic mean (CV %) only

A randomized, single dose (1 x 750 mg), blinded, 2-way crossover comparative bioavailability study of APO-NAPROXEN SR (Apotex Inc.) and NAPROSYN SR (Syntex Inc.) was conducted in healthy male volunteers under fasting conditions. A summary of the comparative bioavailability data from 14 volunteers that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Naproxen (1 x 750 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg•h/mL)	1342.1 1365.8(17.9)	1323.4 1336.0 (13.7)	101.4	93.2 – 110.4
AUC_{0-24} (mcg•h/mL)	685.1 696.4 (19.4)	716.7 732.2 (18.5)	95.6	88.6 – 103.1
AUC_I (mcg•h/mL)	1467.3 1493.6 (17.7)	1469.8 1487.5 (13.1)	99.8	94.1 – 105.9
C_{max} (mcg/mL)	39.0 39.9 (18.4)	41.7 42.7 (23.6)	93.4	87.8 – 99.5

Naproxen (1 x 750 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
T_{max}[3] (h)	15.1 (60.3)	11.2 (75.3)		
$T_{½}$[3] (h)	16.7 (13.6)	16.8 (15.2)		
[1] APO-NAPROXEN SR (naproxen) tablets, 750 mg (Apotex Inc.) [2] NAPROSYN SR (naproxen) tablets, 750 mg (Syntex, Inc. Canada) [3] Expressed as arithmetic mean (CV %) only				

A randomized, single dose (1 x 750 mg), blinded, 2-way crossover comparative bioavailability study of APO-NAPROXEN SR (Apotex Inc.) and NAPROSYN SR (Syntex Inc.) was conducted in healthy male volunteers under fed conditions. A summary of the comparative bioavailability data from 16 volunteers that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Naproxen (1 x 750 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg•h/mL)	1491.1 1524.1 (20.8)	1420.7 1459.7 (20.4)	105.0	100.8 – 109.3
AUC_{0-24} (mcg•h/mL)	1011.9 1021.1 (13.4)	991.0 1004.8 (11.7)	102.1	99.4 – 104.9
AUC_I (mcg•h/mL)	1606.5 1642.4 (20.7)	1539.2 1581.1 (20.3)	104.4	100.4 – 108.5
C_{max} (mcg/mL)	74.3 75.3 (15.7)	78.6 79.9 (13.6)	94.5	90.0 – 99.3
T_{max}[3] (h)	5.8 (20.1)	5.7 (19.0)		
$T_{½}$[3] (h)	15.0 (18.7)	14.8 (21.2)		
[1] APO-NAPROXEN SR (naproxen) tablets, 750 mg (Apotex Inc.) [2] NAPROSYN SR (naproxen) tablets, 750 mg (Syntex, Inc. Canada) [3] Expressed as arithmetic mean (CV %) only				

A multiple dose (1 x 750 mg administered once daily for 7 days), 2-way crossover comparative bioavailability study of APO-NAPROXEN SR (Apotex Inc.) and NAPROSYN SR (Syntex Inc.) was conducted in healthy male volunteers. A summary of the comparative bioavailability data from 14 volunteers that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Naproxen (1 x 750 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{tau} (mcg•h/mL)	1163.5 1181.3 (17.6)	1195.1 1210.0 (16.1)	97.4	88.1 – 107.6
C_{max} (mcg/mL)	67.5 69.0 (21.6)	70.2 70.9 (14.4)	96.1	86.5 – 106.9
C_{min} (mcg/mL)	32.6 33.8 (26.5)	32.8 33.5 (19.5)	99	86.9 – 113.9
T_{max}[3] (h)	4.21 (19.0)	4.21 (36.3)		

[1] APO-NAPROXEN SR (naproxen) tablets, 750 mg (Apotex Inc.)
[2] NAPROSYN SR (naproxen) tablets, 750 mg (Syntex, Inc. Canada)
[3] Expressed as arithmetic mean (CV %) only

A single dose (1 x 500 mg), 2-way crossover comparative bioavailability study of APO-NAPROXEN EC (Apotex Inc.) and NAPROSYN E (Hoffmann-La Roche Ltd.) was conducted in healthy volunteers under fasting conditions. A summary of the comparative bioavailability data from 16 volunteers that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Naproxen (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg•h/mL)	1133.0 1141.3 (12.4)	1047.3 1071.2 (19.4)	108.2	98.5 – 118.8
AUC_I (mcg•h/mL)	1203.5 1214.8 (14.1)	1113.8 1143.4 (21.5)	108.0	98.4 – 118.6

Naproxen (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
C_{max} (mcg/mL)	61.6 62.6 (17.6)	60.0 62.5 (26.7)	102.6	91.8 – 114.7
T_{max}[3] (h)	4.5 (3.5 – 12.0)	4.5 (2.0 – 16.0)		
$T_{½}$[4] (h)	17.1 (11.8)	17.3 (15.5)		
[1] APO-NAPROXEN EC (naproxen) tablets, 500 mg (Apotex Inc.) [2] NAPROSYN E (naproxen) tablets, 500 mg (Hoffmann-La Roche Ltd., Canada) [3] Expressed as median (range) only [4] Expressed as arithmetic mean (CV %) only				

A single dose (1 x 500 mg), 2-way crossover comparative bioavailability study of APO-NAPROXEN EC (Apotex Inc.) and NAPROSYN E (Hoffmann-La Roche Ltd.) was conducted in healthy volunteers under fed conditions. A summary of the comparative bioavailability data from 14 volunteers that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Naproxen (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg•h/mL)	1052.6 1087.9 (25.0)	1100.3 1123.1 (20.5)	96.6	87.8 – 106.2
AUC_I (mcg•h/mL)	1158.5 1208.4 (28.8)	1219.1 1259.7 (26.7)	96.0	87.5 – 105.3
C_{max} (mcg/mL)	59.3 60.6 (20.8)	61.7 62.7 (16.5)	96.3	85.0 – 109.1
T_{max}[3] (h)	12.0 (8.0 – 24.0)	12.0 (3.0 – 24.0)		
$T_{½}$[4] (h)	17.0 (17.9)	17.6 (19.1)		

Naproxen (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
[1] APO-NAPROXEN EC (naproxen) tablets, 500 mg (Apotex Inc.) [2] NAPROSYN E (naproxen) tablets, 500 mg (Hoffmann-La Roche Ltd., Canada) [3] Expressed as median (range) only [4] Expressed as arithmetic mean (CV %) only				

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Animal Toxicity

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

Hamster	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 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 1 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 condition, 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.

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.

Genotoxicity

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

Reproductive and Developmental Toxicology

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.

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. NAPROSYN®, (Naproxen; 375 mg & 500 mg Enteric-Coated Tablets and 750 mg Sustained-Release Tablet), submission control 255330, Product Monograph, Atnahs Pharma UK Limited. (JAN 10, 2022).

2. NAPROSYN®, (Naproxen; 250 mg, 375 mg & 500 mg Film-Coated Tablets, 250 mg, 375 mg & 500 mg Enteric-Coated Tablets, 750 mg & 1000 mg Sustained-Release Tablet), 25 mg/mL Suspension, and 500 mg Suppositories), submission control 035645, Product Monograph, Hoffmann-La Roche Limited. (MAY 10, 1995).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-NAPROXEN
Naproxen Tablets

PrAPO-NAPROXEN SR
Naproxen Sustained-Release Tablets

PrAPO-NAPROXEN EC
Naproxen Enteric-Coated Tablets

Read this carefully before you start taking **APO-NAPROXEN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-NAPROXEN**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- APO-NAPROXEN can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take APO-NAPROXEN for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or had heart problems, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- APO-NAPROXEN can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Talk to your healthcare professional about any medical conditions you have and drugs you are taking.

Pregnancy:

- **DO NOT** take APO-NAPROXEN if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) only take APO-NAPROXEN if you are told to do so by your healthcare professional.
- Medicines like APO-NAPROXEN may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe APO-NAPROXEN during

this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with APO-NAPROXEN.

What is APO-NAPROXEN used for?

APO-NAPROXEN is used in adults to:

- Treat the signs and symptoms of arthritis disorders such as:
  - Osteoarthritis
  - Rheumatoid arthritis
  - Ankylosing spondylitis
- help relieve:
  - minor aches and pains in muscles, bones and joints
  - mild to moderate pain with inflammation in sprains and strains and period cramps (primary dysmenorrhea).

How does APO-NAPROXEN work?

- APO-NAPROXEN (naproxen) belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It can reduce the chemicals produced by your body which cause pain and swelling.
- APO-NAPROXEN only treats the symptoms and relieves pain and inflammation as long as you take it. APO-NAPROXEN does not cure the illness or stop it from getting worse.

What are the ingredients in APO-NAPROXEN?

Medicinal ingredients: naproxen

Non-medicinal ingredients:

- APO-NAPROXEN (immediate release) tablets: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and methylcellulose. The 250 and the 500 mg tablets also contain D&C yellow #10 and FD&C yellow #6; the 375 mg tablets contain only FD&C yellow #6; the 125 mg tablets contain D&C yellow #10 and FD&C blue #2.
- APO-NAPROXEN SR (sustained-release) tablets: D&C yellow #10, FD&C yellow #6, hydroxypropyl methylcellulose and magnesium stearate.
- APO-NAPROXEN EC (enteric-coated) tablets: colloidal silicon dioxide, croscarmellose sodium, hydroxyethyl cellulose, magnesium stearate, methacrylic acid copolymer, methylcellulose, polyethylene glycol, talc, titanium dioxide and triethyl citrate.

APO-NAPROXEN comes in the following dosage forms:

- immediate release tablets (125 mg, 250 mg, 375 mg and 500 mg)
- enteric coated tablets (250 mg, 375 mg and 500 mg)
- sustained-release tablets (750 mg)

Do not use APO-NAPROXEN if you:

- have heart bypass surgery (planning to have or recently had).
- have severe, uncontrolled heart failure.
- are bleeding in the brain or other bleeding disorders.
- are pregnant and in a later stage of pregnancy (28 weeks or later).
- are currently breastfeeding (or planning to breastfeed).
- are allergic to naproxen or any of the other ingredients in this medicine or the container.
- have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking acetylsalicylic acid (ASA) or other NSAIDs.
- have active stomach or intestine ulcers.
- have active bleeding from the stomach or gut.
- have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- have liver disease (active or severe).
- have kidney disease (severe or worsening).
- have high potassium in the blood.
- are under 18 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-NAPROXEN. Talk about any health conditions or problems you may have, including if you:

- Have high blood pressure, high cholesterol or diabetes
- Have or had heart attacks, chest pain, heart disease, stroke or heart failure
- Have poor blood flow to your extremities (like your hands and feet)
- Smoke or used to smoke
- Drink a lot of alcohol
- Have a stomach infection
- Have liver or kidney problems, urine problems or are dehydrated
- Have a history of ulcer or bleeding from the stomach or gut (small or large intestine)
- Have other bleeding or blood problems
- Have asthma
- Are pregnant, planning on becoming or become pregnant while taking APO-NAPROXEN.
- Have immune system problems

Other warnings you should know about:

Serious Side Effects: APO-NAPROXEN can cause serious side effects, including:

- **Blood and bleeding problems:**
  - APO-NAPROXEN can cause blood problems, bleeding and prolonged bleeding.
  - Taking APO-NAPROXEN with the following drugs can increase the risk of bleeding:
    - anticoagulants (prevents blood clots), corticosteroids (anti-inflammatory) or antidepressants like selective serotonin reuptake inhibitors (SSRIs).

- **Serious skin reactions:** In rare cases, serious, life-threatening allergic and skin reactions have been reported with some NSAIDs, such as APO-NAPROXEN. These skin problems most often happen during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment.

  APO-NAPROXEN might cause you to become more sensitive to sunlight. Sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, talk to your healthcare professional.

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with APO-NAPROXEN to monitor your health. They will:

- Check your blood pressure.
- Check your eyes. APO-NAPROXEN can cause blurred or reduced vision.
- Do blood and urine tests to check your liver, kidney and blood health.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and Using Machines: APO-NAPROXEN may cause eye or nervous system problems. This includes tiredness, trouble sleeping, blurred vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or doing activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking APO-NAPROXEN, do NOT drive or operate machinery.

Fertility in Women: APO-NAPROXEN may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking APO-NAPROXEN. Talk to your healthcare professional if you have questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of APO-NAPROXEN. They will monitor your health during and after treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-NAPROXEN:

- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation, like:
  - celecoxib, diclofenac, ibuprofen, naproxen
- Antacids, used to treat symptoms of excess stomach acid
- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline, and lithium
- Medicines used to treat high blood pressure like enalapril, ramipril, candesartan, irbesartan, propranolol
- Medicines used as blood thinners or to prevent blood clots, like warfarin, ASA, clopidogrel
- Medicines used to lower extra fluid levels (diuretics), like furosemide, hydrochlorothiazide
- Medicines used to treat diabetes, like sulphonylurea or other oral hypoglycemics
- Medicines used to treat bacteria infections (antibiotics) like quinolone or sulphonamide
- Medicines used to lower the risk of organ rejection, like tacrolimus and cyclosporin
- Corticosteroids (including glucocorticoids such as prednisone), used as an anti-inflammatory
- Cholestyramine, used to lower cholesterol levels
- Digoxin, used to treat heart disorders
- Hydantoin, used to treat seizures
- Medicines used to treat different cancers, like methotrexate and pemetrexed
- Oral birth control, used to prevent pregnancy
- Probenecid, used to prevent gout
- Alcohol

How to take APO-NAPROXEN:

- Take exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- Swallow capsules whole with food or milk. Do NOT split, chew or crush the tablets.
- **This medicine has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.**
- If you will be taking APO-NAPROXEN for more than 7 days, see your healthcare professional regularly. They will check if APO-NAPROXEN is working for you and if it is causing any side effects.

Usual dose:

Adults 18 years and older:

- Your healthcare professional will decide on the best dosage for you based on your condition.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
    - experience serious side effects, or
    - your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-NAPROXEN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of APO-NAPROXEN, take the dose as soon as possible. Take your next dose at the usual time.
- If it is close to the time of your next dose, skip the missed dose. Take your next dose at the usual time.
- Do not take two doses at the same time to make up for a forgotten dose.

What are possible side effects from using APO-NAPROXEN?

These are not all the possible side effects you may have when taking APO-NAPROXEN. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, diarrhea, constipation, stomach upset/abdominal pain, heartburn, indigestion, feeling gassy
- Headache, dizziness, light-headedness
- Feeling of burning/prickliness/numbing
- Confusion, hard to concentrate or think, short-term memory loss, nervousness
- Bruises
- Skin rash
- Taste disorder, thirst, dry mouth
- Muscle pain
- Mouth sores
- Hair loss
- Increased sweating
- Problems with your period (women)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever		√	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	√		
UNCOMMON			
Anaphylaxis/hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock			√
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): Headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness		√	
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		√	
Congestive heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Depression (sad mood that will not go away): difficulty sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide.		√	
Kidney disorder/problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)		√	
Liver problems (including hepatitis, liver failure, cholestasis): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		√	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			√
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			√
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		√	
Vertigo (a sense of severe spinning dizziness, lightheadedness)		√	
RARE			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, hives, red or dry itchy skin, purple or red spots on skin			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 30°C). Store in a dry place.
Do NOT keep expired medicine or medicine no longer needed. Return to your healthcare professional.
Keep out of reach and sight of children.

If you want more information about APO-NAPROXEN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

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