PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] ETODOLAC

Etodolac capsules

Capsule, 200 mg and 300 mg, for oral use

BP

Non-Steroidal Anti-Inflammatory Drug (NSAID)

Apotex Inc.

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Toronto, Ontario,

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RECENT MAJOR LABEL CHANGES

2 Contraindications	09/2022
3 Serious Warnings and Precautions Box	09/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ETODOLAC (Etodolac capsules) is indicated for:

- acute or long–term use in the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis (degenerative joint disease).

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 ETODOLAC 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.

ETODOLAC, as a NSAID, does NOT treat clinical disease or prevent its progression.

ETODOLAC, 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 ETODOLAC 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 post market 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

ETODOLAC is contraindicated in:

- Patients who are hypersensitive to ETODOLAC or to other NSAIDs 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.
- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although ETODOLAC 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.
- 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 ETODOLAC 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):**

  ETODOLAC 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 ETODOLAC 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 ETODOLAC, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. See 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance.

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

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

  Use of NSAIDs, such as ETODOLAC, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

- **Risk in Pregnancy:**

  Caution should be exercised in prescribing ETODOLAC during the first and second trimesters of pregnancy. Use of NSAIDS 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). ETODOLAC is contraindicated for use during the third trimester of pregnancy 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 ETODOLAC 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.**
- Caution should be exercised in prescribing ETODOLAC 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.
- A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients.

4.2 Recommended Dose and Dosage Adjustment

Use of ETODOLAC 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.

Adults

The recommended dosage of ETODOLAC in the treatment of rheumatoid arthritis and osteoarthritis is 200 to 300 mg twice daily. Patients may also respond to a single daily (400 mg or 600 mg) dose administered in the evening.

The safety of doses in excess of 1000 mg per day for extended periods has not been established. In order to maximize the effectiveness of therapy, the dosage must be individualized for each patient.

Pediatric Use (<18 years of age):

Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS.

Geriatrics (≥ 65 years of age)

As with any NSAID, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In otherwise healthy patients 65 years and older, no substantial differences in the side-effects profile of etodolac were seen. See 7.1.4 Geriatrics.

Renal impairment: A lower dose should be considered in patients with mild and moderate renal impairment. ETODOLAC 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. ETODOLAC is contraindicated in severe liver impairment or active liver disease. See 2 CONTRAINDICATIONS.

4.4 Administration

ETODOLAC should be taken with meals to minimize gastrointestinal intolerance.

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 etodolac 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.

One case of intentional etodolac overdosage has been reported. This 53–year–old female ingested from 15 to 46 two hundred mg etodolac capsules (3 to 8.6 grams). Plasma etodolac concentrations were measured frequently over the next 4 days. At 5 hours after ingestion (3 hours after gastric lavage) the plasma etodolac level was 22 μg/mL. These plasma levels and her subsequent recovery with no signs or symptoms of etodolac toxicity were consistent with systemic absorption of 600 to 800 mg. Her laboratory tests on admission showed a prolonged prothrombin time and a false–positive urine bilirubin (attributed to the phenolic etodolac metabolites).

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	Capsules 200 mg, 300 mg	Black iron oxide, colloidal silicon dioxide, croscarmellose sodium, edible ink, erythrosine aluminum lake, gelatin, iron oxide yellow, lactose monohydrate, propylene glycol, shellac, stearic acid, talc, titanium dioxide and yellow iron oxide.

Description

ETODOLAC 200 mg Capsules: Each hard gelatin capsule consists of a dark grey opaque body, and a light grey opaque cap, imprinted "200" in red, with a white powder fill. Each capsule contains 200 mg etodolac. Available in bottles of 100.

ETODOLAC 300 mg Capsules: Each hard gelatin capsule consists of a light grey opaque body, light grey opaque cap, imprinted "300" in red ink, with a white powder fill. Each capsule contains 300 mg etodolac. Available in bottles of 100.

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.

ETODOLAC 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.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

ETODOLAC 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 ETODOLAC 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 ETODOLAC, 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 ETODOLAC should hypertension either develop or worsen with its use.

Use of NSAIDs, such as ETODOLAC, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).

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

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.

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

Endocrine and Metabolism

Glucose and lipid metabolism

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Corticosteroids: ETODOLAC 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, perforation, obstruction and 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 ETODOLAC. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care professionals should remain alert for ulceration and bleeding in patients treated with ETODOLAC, 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 ETODOLAC and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2 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 ETODOLAC 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)

If peptic ulceration is suspected or confirmed or if gastrointestinal bleeding or perforation occurs in patients under treatment with ETODOLAC, the drug should be immediately withdrawn, an appropriate treatment initiated and the patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2–receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of ETODOLAC therapy when and if the adverse reactions appear.

ETODOLAC should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, melena, diverticulosis or other inflammatory disease of the gastrointestinal tract (such as ulcerative colitis or Crohn's disease). In these cases the physician must weigh the benefits of treatment against the possible hazards (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur at any time during treatment, without warning symptoms or signs.

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 ETODOLAC 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 ETODOLAC is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of ETODOLAC 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.

ETODOLAC 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 (ASA) or other NSAIDs.

Concomitant administration of ETODOLAC 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 ETODOLAC. 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 ETODOLAC, 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.

Meaningful (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) occurred in controlled clinical trials with etodolac in approximately 1% of patients.

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

Infection: ETODOLAC, 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 professional must be vigilant to the development of this complication.

Monitoring and Laboratory Tests

Cardiovascular: Patients on long-term treatment with ETODOLAC should have their blood pressure monitored regularly and an ophthalmic examination should be carried out at periodic intervals. See 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG INTERACTIONS.

Hematology: Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should be checked in patients on long-term treatment with ETODOLAC. Additionally, concurrent therapy with anticoagulants requires close monitoring of the international normalized ratio (INR). See 7 WARNINGS AND PRECAUTIONS, Hematologic and 9 DRUG INTERACTIONS.

Lithium plasma concentration (in case of lithium co-prescription) should be monitored. See 9.4 Drug-Drug Interactions, Lithium.

Hepatic: Serum transaminase and bilirubin should be monitored regularly during ETODOLAC treatment. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

Pregnancy: If ETODOLAC is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on ETODOLAC be closely monitored for amniotic fluid volume since ETODOLAC may result in reduction of amniotic fluid volume and even oligohydramnios (see 7.1 Special Populations). ETODOLAC is contraindicated for use in the third trimester of pregnancy. See 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy and 7.1.1 Pregnant women.

Renal: Serum creatinine, creatinine clearance and serum urea should be monitored in patients during ETODOLAC treatment. Electrolytes including serum potassium should be monitored. See 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Renal and 9 DRUG INTERACTIONS.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as ETODOLAC. 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 ETODOLAC and other NSAIDs. If such symptoms develop ETODOLAC should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving ETODOLAC for an extended period of time.

Peri-Operative Considerations

See 2 CONTRAINDICATIONS - Coronary Artery Bypass Graft Surgery.

Psychiatric

See 7 WARNINGS AND PRECAUTIONS, Neurologic.

Renal

Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II 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 ETODOLAC, 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 ETODOLAC, 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 ETODOLAC in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Use of NSAIDs, such as ETODOLAC, 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 ETODOLAC, 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 ETODOLAC should be considered.

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 ETODOLAC. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving ETODOLAC. ETODOLAC 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: ETODOLAC 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 ETODOLAC, 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

ETODOLAC 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-CLINICAL TOXICOLOGY.

Caution is recommended in prescribing ETODOLAC 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 ETODOLAC 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-fetal 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-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis period.

ETODOLAC 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. See 2 CONTRAINDICATIONS.

7.1.2 Breast-feeding

ETODOLAC is contraindicated in women who are breastfeeding. 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 ETODOLAC 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 seve ral 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.

Adverse reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double–blind and open–label clinical trials of 4 to 320 weeks in duration and worldwide post–marketing surveillance studies in approximately 60,000 patients.

In clinical studies, etodolac was generally well tolerated. Most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials because of adverse events, was 9% for patients treated with etodolac.

Listed below are the patient complaints with an incidence of greater than, equal to, or less than 1% which occurred in clinical trials and post–marketing experience with etodolac at doses up to 1000 mg per day.

Table 2 - Adverse reactions reported with ETODOLAC

	(≥1%)
Ear and labyrinth disorders	tinnitus
Eye disorders	blurred vision
Gastrointestinal disorders	nausea; diarrhea; epigastric pain; heartburn; indigestion; flatulence; abdominal pain; gastrointestinal cramps; abdominal distention; constipation; vomiting; dyspepsia; gastritis; melena
General disorders and administration site conditions	fatigue; weakness/malaise
Metabolism and nutrition disorders	fluid retention/edema
Nervous system disorders	headache; dizziness; drowsiness; insomnia
Psychiatric disorders	nervousness/anxiety; depression
Renal and urinary disorders	urinary frequency; dysuria

	(≥1%)
Skin and subcutaneous tissue disorders	dermatitis manifested as skin rash (erythematous, vesicular, maculopapular, morbilliform, petechial, or eczematous), or pruritus

8.3 Less Common Clinical Trial Adverse Reactions

Table 3 - Adverse reactions reported with ETODOLAC

	(<1%)
Blood and lymphatic system disorders	agranulocytosis; pancytopenia; anemia; hemolytic anemia; thrombocytopenia; leukopenia; neutropenia; eosinophilia
Cardiac disorders	congestive heart failure; palpitations; tachycardia; chest pain (costal, costochondral, or retrosternal); arrhythmias; myocardial infarction; and chest tightness or fullness
Ear and labyrinth disorders	hearing loss, ear ache, pressure/throbbing in ears
Eye Disorders	visual disturbances including teichopsia; burning sensation of eyes; twinging behind eyes; photophobia; conjunctivitis
Gastrointestinal disorders	peptic ulcer with/without gastrointestinal hemorrhage and/or perforation; hematemesis; rectal bleeding; stool changes (loose, with mucus, or increase in number and/or frequency); taste abnormalities including loss of taste; eructation; stomatitis; esophagitis with or without erosions or stricture or cardiospasm; colitis; pancreatitis; sore, dry, inflamed or swollen mucous membranes including mouth, tongue, and lips
General disorders and administration site conditions	tenderness, pyrexia; chills; lethargy; general deterioration; flushing; hot flashes; diaphoresis
Hepatobiliary disorders	hepatitis; cholestasis; jaundice

	(<1%)
Immune system disorders	anaphylactic/anaphylactoid reaction; laryngeal edema
Investigations	elevated hepatic enzymes; increased serum creatinine; decreased hemoglobin; decreased hematocrit; atypical lymphocytes; increased bleeding time
Metabolism and nutrition disorders	change in weight; change in appetite; anorexia; excessive thirst
Musculoskeletal and connective tissue disorders	muscle cramps; muscular fatigue; pain in arms/hands/shoulders; tenderness; subcutaneous nodule/first metatarsophalangeal joint
Nervous system disorders	restlessness; confusion; vertigo; syncope; inability to concentrate, somnolence; paraesthesia; involuntary muscle movement; hand tremor
Psychiatric disorders	nightmares; listlessness
Renal and urinary disorders	dysuria; urinary urgency; hematuria; nocturia; cystitis; renal calculus; interstitial nephritis; papillary necrosis; renal failure
Reproductive system and breast disorders	breast tenderness; vaginal bleeding; difficulty maintaining erection; recto–pubic pain; leukorrhea; uterine bleeding irregularities
Respiratory, thoracic and mediastinal disorders	dyspnea; asthma; bronchospasm; hyperventilation; sneezing and sighing; bronchitis; pharyngitis; rhinitis; sinusitis; epistaxis; burning sensation of nose
Skin and subcutaneous tissue disorders	urticaria; angioedema; alopecia; photosensitivity; peeling; easy bruising; brittle nails; exfoliative dermatitis; Stevens–Johnson syndrome, cutaneous vasculitis with purpura; erythema multiforme
Vascular Disorders	vasculitis; hypertension

8.5 Post-Market Adverse Reactions

Additional reports of serious adverse events temporally associated with ETODOLAC 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 ETODOLAC exposure.

Blood and lymphatic system disorders- Agranulocytosis, hemolytic anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia.

Gastrointestinal disorders - Duodenitis, intestinal ulceration, pancreatitis.

Hepatobiliary disorders – Cholestatic hepatitis, hepatitis, cholestatic jaundice, jaundice, hepatic failure, liver necrosis, fatal fulminant hepatitis.

Immune system disorders - Allergic reaction, anaphylactic/anaphylactoid reactions (including shock).

Investigations - Elevated BUN

Metabolism and nutrition disorders - Hyperglycemia in previously controlled diabetic patients.

Renal and urinary disorders - Renal failure, renal insufficiency, renal papillary necrosis.

Respiratory, thoracic and mediastinal disorders - Pulmonary infiltration with eosinophilia.

Skin and subcutaneous tissue disorders - Cutaneous vasculitis with purpura, Stevens-Johnson Syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis, erythema multiforme.

Vascular disorders - Vasculitis (including necrotizing and allergic).

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	CT	• The concomitant use of	• Concomitant use of

Proper/Common name	Source of Evidence	Effect	Clinical comment
(ASA) or other NSAIDs		ETODOLAC 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. • Some NSAIDs (e.g. ibuprofen and naproxen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.	ETODOLAC and analgesic doses of ASA or other NSAIDs is not recommended because of the increased risk of bleeding. See 7 WARNINGS AND PRECAUTIONS
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
Albumin-Bound Drugs	T	• Etodolac is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other	• Patients should be under careful observation for adjustment of dose if required.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		albumin-bound drugs such as coumarin-type anticoagulants, warfarin, sulfonamide or sulphonylureas, hydantoins, other NSAIDs, and ASA.	
Antacids	N/A	• Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of etodolac.	• Concomitant administration is not recommended.
Anti-coagulants	CT	• Etodolac and anticoagulants such as warfarin have a synergistic effect on bleeding. • The concomitant use of etodolac 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
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 etodolac.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS
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 etodolac.	• Concomitant administration is not recommended.
Digoxin	C	• The concomitant use of etodolac with digoxin has been reported to increase the serum concentration	• Monitor serum digoxin levels.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		and prolong the half-life of digoxin which may result in digitalis toxicity.	
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 ETODOLAC 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 etodolac 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
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 etodolac, 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

The urine of patients who take etodolac can give a false–positive reaction for urinary bilirubin (urorubin) due to the presence of phenolic metabolites of etodolac.

Diagnostic dip–stick methodology, used to detect ketone bodies in urine, has resulted in false–positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose–relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1-2 mg% were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to one year of therapy.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Etodolac is a nonsteroidal anti–inflammatory drug (NSAID) that exhibits anti–inflammatory, analgesic and antipyretic properties in animal models. The pharmacological actions of etodolac are thought to be related to inhibition of prostaglandin biosynthesis at the site of inflammation.

ETODOLAC is a racemic mixture of R– and S–etodolac. As with other NSAIDs, it has been demonstrated in animals that the S-form is biologically active and the R– form is not. Both enantiomers are stable and there is no R–to–S conversion *in vivo*.

10.2 Pharmacodynamics

Special Studies

Etodolac was compared to other NSAIDs in studies focusing on gastrointestinal (GI) microbleeding, endoscopy, and gastroduodenal prostaglandin assays. The clinical significance of these results is unknown.

In gastrointestinal microbleeding studies of healthy individuals, the GI blood loss observed with etodolac (600 mg to 1200 mg per day) was similar to that seen with placebo and significantly less than that seen with acetylsalicylic acid (ASA) (2600 mg per day), ibuprofen (2400 mg per day), indomethacin (200 mg per day), or naproxen (750 mg per day). In a study of etodolac (600 mg and 1000 mg per day) and piroxicam (20 mg per day), GI blood loss observed with etodolac was comparable with that seen with placebo and significantly less than that seen with piroxicam.

With endoscopy studies in healthy volunteers, etodolac treatment (up to 1200 mg per day) resulted in endoscopy scores which were similar to baseline and placebo, and significantly better than following treatment with ASA (3900 mg per day), ibuprofen (2400 mg per day), indomethacin (200 mg per day), or naproxen (1000 mg per day). The effects of etodolac (600 mg to 1200 mg per day) and diclofenac (150 mg per day) were not significantly different from each other or from baseline, as shown by endoscopy. GI microbleeding and endoscopy studies provide an objective measure of blood loss and lesions.

Prostaglandin assays of the gastroduodenal mucosa of patients with active rheumatoid arthritis were performed in a double-blind randomized study involving therapeutic doses of etodolac (600 mg per day) and naproxen (1000 mg per day). Biopsies were taken at baseline and after

4 weeks of treatment. The results of this study indicate that etodolac does not appear to affect gastric or duodenal prostaglandin synthesis.

10.3 Pharmacokinetics

Absorption

Etodolac is well absorbed following oral administration. The systemic availability of etodolac is at least 80%, and the drug does not undergo significant first–pass metabolism.

Distribution

The dose–proportionality based on AUC (the area under the plasma concentration–time curve) is linear following doses up to 600 mg every 12 hours. Etodolac is more than 99% bound to plasma proteins.

Table of Etodolac Steady–State Pharmacokinetic Parameters (n=267)		
Kinetic Parameters	Scientific Notation (Units)	Mean ± SD
Extent Of Oral Absorption (Bioavailability)	F (%)	≥80
Peak Concentration Time	t_{max} (hr)	1.7 ± 1.3
Oral–Dose Clearance	CL/F (mL/hr/kg)	47 ±16
Central Compartment Volume	V_c/F (mL/kg)	132 ±47
Steady–State Volume	V_{ss}/F (mL/kg)	362 ±129
Distribution Half–Life	$t_{½}$ (hr)	0.71 ± 0.50
Terminal Half–Life	$t_{½}$ (hr)	7.3 ± 4.0

Mean peak plasma concentrations range from approximately 14 ±4 to 37 ± 9 mcg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes. The mean plasma clearance of etodolac is 47 (±16) mL/hr/kg, and terminal disposition half–life is 7.3 (± 4.0) hours.

Metabolism

Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

Etodolac, unchanged	1%
Etodolac glucuronide	13%
Hydroxylated metabolites (6–, 7– and 8–OH)	5%
Hydroxylated metabolite glucuronides	20%
Unidentified metabolites	33%

Elimination

Fecal excretion accounted for 16% of the dose. Therefore, enterohepatic circulation, if present, is not extensive.

Special Populations and Conditions

The extent of absorption of etodolac is not affected when it is administered after a meal or with an antacid. Food intake, however, reduces the peak concentration reached by approximately one–half, and increases the time–to–peak concentration by 1.4 to 3.8 hours. Co–administration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time–to–peak.

- **Geriatrics:** In studies in the elderly, age was found to have no effect on etodolac half-life or protein binding, and there was no drug accumulation. Etodolac clearance was reduced by about 15%. Because the reduction in clearance is small, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size, and they may be more sensitive to antiprostaglandin effects than younger patients.
- **Hepatic Insufficiency:** In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.
- **Renal Insufficiency:** In studies of the effects of mild to moderate renal impairment, no significant differences in the disposition of total and free etodolac were observed. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable. No adjustment of etodolac is generally required in patients with mild to moderate renal impairment; however, etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C) and protect from moisture.

Keep out of reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

N/A

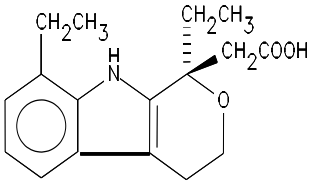
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Etodolac
Chemical name:	(1RS)-1,8–Diethyl–1,3,4,9–tetrahydropyrano[3,4-b]indol–1–acetic acid
Molecular formula and molecular mass:	$C_{17}H_{21}NO_3$ and 287.4

Structural formula:



and enantiomer

Physicochemical properties:	Etodolac is a white to almost white crystalline powder. Practically insoluble in water, freely soluble in ethanol (96%).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Rheumatoid arthritis and osteoarthritis

Etodolac has been studied in double–blind, randomized, parallel–group, multicentre clinical trials in the treatment of rheumatoid arthritis and osteoarthritis. In rheumatoid arthritis studies, etodolac 200 mg twice a day was compared with naproxen 500 mg twice a day, piroxicam 20 mg once a day, or diclofenac 50 mg three times a day. In osteoarthritis studies, etodolac 200 mg three times a day was compared with diclofenac 50 mg three times a day, and etodolac 300 mg twice a day was compared with piroxicam 20 mg once a day, or naproxen 500 mg twice a day.

Results of these rheumatoid arthritis and osteoarthritis studies showed etodolac to be comparable to naproxen, piroxicam and diclofenac. Key efficacy parameters improved significantly ($p<0.05$) in all treatment groups with no significant differences between therapies.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of ETODOLAC 300 mg capsules (Apotex Inc.) and Ultradol® 300 mg capsules (Procter & Gamble Pharmaceuticals Canada Inc.) was conducted in 24 healthy adult human male subjects under fasting conditions. Comparative bioavailability data from 23 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Etodolac (1 x 300 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg·h/mL)	93.34 97.25 (30)	96.58 100.99 (31)	96.6	92.6 – 100.9
AUC_I (mcg·h/mL)	96.15 100.88 (34)	99.62 105.20 (36)	96.5	92.5 – 100.7
C_{max} (mcg/mL)	17.52 17.80 (18)	19.89 20.76 (28)	88.1	78.0 – 99.4
T_{max}[3] (h)	1.50 (0.75 – 3.00)	1.25 (0.50-4.00)		
$T_{½}$[4] (h)	7.03 (25)	7.12 (30)		

[1] ETODOLAC (etodolac) capsules, 300 mg (Apotex Inc.)

[2] Ultradol® (etodolac) capsules, 300 mg (Procter & Gamble Pharmaceuticals Canada Inc.)

[3] Expressed as Median (Range)

[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 Toxicity

The oral and intraperitoneal (i.p.) LD_{50} was determined in mice and rats. The results are shown in the following table.

LD_{50} (mg/kg) of Etodolac in Mice and Rats		
Species and Route of Administration	LD_{50} mg/kg (95% Confidence Limits)	
	Males	Females
Mouse		
-p.o.	883 (628-1288)	1141 (954-1566)
-i.p.	333 (266-367)	379 (346-409)
Rats		
-p.o.	78 (70-88)	191 (148-257)
-i.p.	116 (99-134)	151 (125-199)
*Mortality appeared to plateau at doses between 950 and 1225 mg/kg and therefore the 95% confidence limits could not be calculated.		

Mouse: Drug–related effects occurring in mice after both oral and i.p. administration were tremors, ataxia, dyspnea, hypoactivity, clonic convulsions, and ptosis. Bradypnea and salivation were seen only after oral administration.

Rat: Drug–related effects observed in rats after both oral and i.p. administration included ataxia, hypoactivity, ptosis, yellow fluid around the genitalia, and poor physical condition. In addition, red pigmentation was seen around the mouth or nose after oral administration, and low carriage was seen after i.p. administration.

Subacute And Chronic Toxicity

Etodolac was administered orally to mice for 18 months at dosages ranging from 0-15 mg/kg; orally to rats for two years with dosages ranging from 0-45 mg/kg.

Mouse: An oral range finding study conducted in the mouse for 21 days showed no drug effect at dosages of 3, 9, 15, or 20 mg/kg. However, in light of drug effects occurring in the first six months of a two year rat study at 9 and 15 mg/kg, it appeared appropriate to limit the dosages for an 18 month mouse study to 3, 9, and 15 mg/kg. This dosage selection was further supported by preliminary drug metabolism data suggesting that rats and mice had similarities in t_{max} values and elimination half-lives.

Eighteen–Month Oral Toxicity Study

After eighteen months of drug administration to mice at dosages ranging from 3 to 15 mg/kg, etodolac was not considered tumorigenic. No drug–related changes occurred in physical

appearance, behaviour, body weight, food consumption, clinical chemistry, or ophthalmologic findings. The lymphocyte to neutrophil ratio was reversed in the 15 mg/kg males, but no other changes occurred in hematologic values.

Males and females in the 15 mg/kg etodolac–treated group had decreased survival. These deaths could not be directly related to the administration of etodolac. No etodolac effects were observed in the 3 and 9 mg/kg groups.

Rats

Two–Year Oral Toxicity Study

Etodolac was considered to be non–tumorigenic after oral administration to rats at dosages ranging from 3 to 15 mg/kg for two years. Adverse effects on survival, general behaviour, and appearance and secondary alterations in hematologic values occurred in the 15 mg/kg group and to a lesser extent in some rats receiving 9 mg/kg. Variations in body weight occurred in the etodolac–treated rats throughout the study; however, at the end of the study, the values were generally comparable to the control values. Etodolac–induced, dosage–related histopathologic lesions of the gastrointestinal tract (ulceration) and kidney (papillary necrosis) occurred in rats receiving 9 and 15 mg/kg, with a few rats at the 3 mg/kg dosage also affected.

Carcinogenicity

Mutagenicity

Etodolac was non–mutagenic in the Salmonella mutagenesis assay (Ames Test), thymidine kinase forward mutation assay using mouse lymphoma cell line L5178Y, *in vivo* micronucleus test using CD–1 mice, and in additional ancillary preliminary supportive studies which included Salmonella mutagenesis assay (Ames Test), *Saccharomyces cerevisiae* D4 gene conversion test, *Schizosaccharomyces pombe* P1 gene mutation assay, unscheduled DNA synthesis assay, reverse mutation assay of urinary etodolac metabolites using *Saccharomyces cerevisiae* D4, and a host mediated assay measuring reverse mutation frequency of *Saccharomyces cerevisiae* D4.

Reproductive and Developmental Toxicology

Fertility Studies in Rats

Oral dosages ranging from 3 to 16 mg/kg of etodolac were used in the Segment I studies. Male and female rat mating performance and pregnancy (i.e., conception) rates were not affected by etodolac treatment at the highest dosage (16 mg/kg). Female treatment resulted in increased pre–implantation loss at dosages of 8 to 16 mg/kg and increased post–implantation loss at dosages of 15 and 16 mg/kg. In fertility studies in which females were allowed to deliver, gestational lengths were increased at dosages of 3 mg/kg and above, and prolonged deliveries, dystocia, and an inability to complete parturition occurred reproducibly at dosages of 9 mg/kg and above; maternal death sometimes accompanied the dystocia. Postnatal pup survival was also reproducibly decreased at dosages of 9 mg/kg and above. The reproductive effects occurred at dosages that also produced maternal gastrointestinal or renal lesions and associated changes in appearance. The effects on parturition and offspring survival in rats are characteristic for drugs that inhibit prostaglandin synthesis.

Teratology Studies

Mouse: A mouse Segment II study conducted at oral dosages ranging from 2 to 10 mg/kg did not reveal an effect of maternal etodolac treatment on offspring *in utero* survival, growth, or morphological development at the highest dosage (10 mg/kg).

Rats: Rat Segment II studies were conducted at oral dosages ranging from 2 to 22 mg/kg. There were no effects of maternal drug treatment on offspring *in utero* survival, growth, or morphological development at the highest dosage (22 mg/kg), although maternal toxicity (e.g. postmortem findings, effects on survival, appearance, body weight gain, and food consumption) was evident at dosages of 6 mg/kg and above. In a Segment II study in which some of the dams from each group were allowed to deliver, there were no effects of maternal gestational drug treatment on offspring postnatal survival, growth, morphological, reflex, or behavioural development or on offspring reproductive performance.

Juvenile Toxicity

Perinatal/Postnatal Studies in Rats

Segment III studies were conducted at oral dosages ranging from 2 to 15 mg/kg. Gestational lengths were increased at dosages of 2 mg/kg and above. Prolonged deliveries, dystocia, inability to complete parturition, and occasional maternal deaths during parturition occurred at dosages of 4 mg/kg and above. Offspring postnatal survival was decreased at dosages of 4 mg/kg and above, accompanied by poor maternal litter care. There were no adverse effects of maternal drug treatment on offspring growth, morphological, reflex, or behavioural development or on offspring reproductive performance. The effects on parturition and offspring survival occurred at dosages that also produced gastrointestinal lesions and were characteristic of drugs such as etodolac, that inhibit prostaglandin synthesis.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrETODOLAC

Etodolac Capsules BP

Read this carefully before you start taking **ETODOLAC** 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 **ETODOLAC**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- ETODOLAC 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 ETODOLAC 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 attacks, chest pain, heart disease, stroke, heart failure, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

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

Pregnancy:

- **DO NOT** take ETODOLAC 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 ETODOLAC if you are told to do so by your healthcare professional. Medicines like ETODOLAC 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 ETODOLAC 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 ETODOLAC.

What is ETODOLAC used for?

ETODOLAC is used in adults to treat the signs and symptoms of arthritis disorders such as:

- Rheumatoid arthritis
- Osteoarthritis

How does ETODOLAC work?

- ETODOLAC 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.
- ETODOLAC only treats the symptoms and relieves pain and inflammation as long as you take it. ETODOLAC does not cure the illness or stop it from getting worse.

What are the ingredients in ETODOLAC?

Medicinal ingredients: etodolac

Non-medicinal ingredients: black iron oxide, colloidal silicon dioxide, croscarmellose sodium, edible ink, erythrosine aluminum lake, gelatin, lactose monohydrate, propylene glycol, shellac, stearic acid, talc, titanium dioxide and yellow iron oxide.

ETODOLAC comes in the following dosage forms:

Capsules: 200 mg and 300 mg

Do not use ETODOLAC if:

- you are planning to have or have recently had heart bypass surgery.
- you have severe, uncontrolled heart failure.
- you have bleeding in the brain or other bleeding disorders.
- you are pregnant and in a later stage of pregnancy (28 weeks or later).
- you are currently breastfeeding (or planning to breastfeed).
- you are allergic to etodolac or any other ingredients in this medicine or part of the container.
- you 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.
- you have active stomach or intestinal ulcers.
- you have active bleeding from the stomach or gut.
- you have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- you have liver disease (active or severe).
- you have kidney disease (moderate, severe or worsening).
- you have high potassium in the blood.
- you are taking other NSAIDs for pain, fever or inflammation.
- you are under 18 years of age.

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

- have a condition that makes you frail or weak.
- have high blood pressure, high cholesterol, diabetes.
- have atherosclerosis. This is when fats and cholesterol build up in your arteries.
- 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.
- have liver or kidney problems, urine problems or are dehydrated.
- are on a low-salt diet.
- have a history of ulcer or bleeding from the stomach or gut (small or large intestines).
- drink a lot of alcohol.
- have a stomach infection.
- have ulcerative colitis or Crohn's disease
- have other bleeding or blood problems.
- have immune system problems.
- have asthma.
- are pregnant, planning on becoming or become pregnant while taking ETODOLAC.
- are taking any other NSAID medicines including acetylsalicylic acid (ASA).
- you are in labour or giving birth
- are lactose intolerant or have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in ETODOLAC.

Other warnings you should know about:

ETODOLAC may cause serious side effects, including:

- **Blood and bleeding problems**:
    - ETODOLAC can cause blood problems, bleeding and prolonged bleeding.
    - Taking ETODOLAC with the following medicines can increase the risk of bleeding:
        - Anticoagulants, which prevent blood clots,
        - corticosteroids, which treat inflammation, 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 ETODOLAC. 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.

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

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.

Fertility in women: ETODOLAC 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 ETODOLAC. Talk to your healthcare professional if you have any 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 ETODOLAC. They will monitor your health during and after treatment.

Driving and using machinery: ETODOLAC 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 ETODOLAC, do NOT drive or operate machinery.

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

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

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 ETODOLAC:

- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation like: celecoxib, diclofenac, ibuprofen, acetaminophen, indomethacin, naproxen, piroxicam, phenylbutazone
- Antacids used to treat symptoms of excess stomach acid including magnesium hydroxide and aluminum hydroxide
- Medicines used as blood thinners to prevent blood clots like warfarin, ASA, clopidogrel
- Medicines used to treat high blood pressure like enalapril, ramipril, candesartan, irbesartan, propranolol, atenolol
- Medicines used to treat bacterial infections like sulfonamides, quinolone antibacterials
- Medicines used to lower the risk of organ rejection like cyclosporine and tacrolimus.
- A medicine used to lower cholesterol levels called cholestyramine.
- A medicine used to treat heart problems called digoxin.
- Medicines used to lower extra fluid levels (called diuretics) like furosemide and hydrochlorothiazide
- Corticosteroids (including glucocorticoids) such as prednisone, used as anti – inflammatory medicines

- Medicines used to treat diabetes, like sulphonylurea or other oral hypoglycaemics like glyburide, glipizide, metformin, chlorpropamide or phenformin, tolbutamide
- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline, and lithium
- Medicines used to treat different cancers like methotrexate and pemetrexed
- Medicines used to treat seizures like phenytoin and hydantoin
- Probenecid used to treat gout
- Alcohol

How to take ETODOLAC:

- Take ETODOLAC exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- You may be told to take your ETODOLAC once per day or twice per day.
- Take ETODOLAC tablets with a meal.
- **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 ETODOLAC for more than 7 days, see your healthcare professional regularly. They will check if ETODOLAC 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 dose that is right for you based on your condition. They will tell you how much to take and how often to take it.
- 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 have serious side effects, or
    - your condition gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much ETODOLAC, 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 ETODOLAC, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and continue with your regular dosing schedule.

Do not take two doses at once to make up for a missed dose.

What are possible side effects from using ETODOLAC?

These are not all the possible side effects you may have when taking ETODOLAC. 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		✓	
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			✓

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**	
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		✓	
Depression (sad mood that will not go away): difficult 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		✓	

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**	
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			✓
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in		✓	

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	
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			✓

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 30ºC). Protect from moisture.

Keep out of reach and sight of children.

Do NOT keep expired medicine or medicine you no longer need. Return any expired or unused medicine to your pharmacist.

If you want more information about ETODOLAC:

- 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) Find the Patient Medication Information on 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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