PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKETOPROFEN

Ketoprofen Capsules BP

Capsule, 50 mg, for oral use

PrKETOPROFEN-E

Ketoprofen Enteric-coated Tablets

Tablet, 50 mg and 100 mg, for oral use

PrKETOPROFEN SR

Ketoprofen Sustained-release Tablets

Tablet, 200 mg, for oral use

Non-Steroidal Anti-inflammatory Drug (NSAID)

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Date of Initial Authorization:
DEC 31, 1989

Date of Revision:
MAY 10, 2022

Submission Control Number: 258038

RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR (Ketoprofen Capsules BP, Ketoprofen Enteric-coated Tablets and Ketoprofen Sustained-release Tablets) are indicated for:

- the treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis,
- the treatment of primary dysmenorrhea,
- the relief of mild to moderate acute pain associated with musculotendinous trauma (sprains and strains), postoperative (including dental surgery) or postpartum pain.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

Use of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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, 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, as NSAIDs, does NOT treat clinical disease or prevent its progression.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, as NSAIDs, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

1.1 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are contraindicated in

- Patients who are hypersensitive to KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 (see 7.1.1 Pregnant women).
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants (see 7.1.2 Breast-feeding).
- Severe uncontrolled heart failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- 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, Immune).
- Active gastric / duodenal / peptic ulcer, active GI bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Severe liver impairment or active liver disease (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- 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 12 years of age.

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)** (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)**.**

  KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are non-steroidal anti-inflammatory drugs (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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR.

- **Risk of Gastrointestinal (GI) Adverse Events** (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

  Use of NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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). KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR should be limited to the lowest effective dose for the shortest possible duration of treatment (see 1 INDICATIONS).
- A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see 4.2 Recommended Dose and Dosage Adjustment).

4.2 Recommended Dose and Dosage Adjustment

Adults

Rheumatoid arthritis and osteoarthritis

The usual dosage for KETOPROFEN capsules or KETOPROFEN-E enteric-coated tablets is 150 to 200 mg per day in 3 or 4 divided doses.

Once the maintenance dosage has been established, patients may be tried on a twice daily dosing regimen. Clinical trials, however, show that some rheumatoid arthritis patients respond better to more frequent dosing. The usual maintenance dose is 100 mg twice daily.

Patients with rheumatoid arthritis or osteoarthritis on a maintenance dose of 200 mg/day may be changed to a once daily dose of KETOPROFEN SR 200 mg tablets administered in the morning or evening. KETOPROFEN SR tablets should be swallowed whole.

KETOPROFEN-E and KETOPROFEN SR tablets provide alternative presentations for those who may prefer these dosage forms. No difference in toxicity profile was documented.

The total daily dose of KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR capsules or tablets should not exceed 200 mg per day. When the patient's response warrants it, the dose may be decreased to the minimum effective level.

In severe cases during a flare-up of rheumatic activity or if a satisfactory response cannot be obtained with the lower dose, a daily dosage in excess of 200 mg may be used, but a dose of 300 mg/day should not be exceeded.

Primary dysmenorrhea and mild to moderate pain

The usual dose for KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR is 25 to 50 mg 3 or 4 times daily as necessary.

A larger dose may be tried if the patient's response to a previous dose was less than satisfactory, but individual doses above 50 mg have not been shown to give added analgesia. The total daily dose should not exceed 300 mg. In most types of acute pain, a course of 3 to 7 days has been shown to be sufficient.

Pediatrics (< 12 years of age): Health Canada has not authorized an indication for pediatric patients. 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.

Initial dosage should be reduced by 1/2 to 1/3 in the elderly.

Renal Impairment

Initial dosage should be reduced by 1/2 to 1/3 in patients with impaired renal function. KETOPROFEN, KETOPROFEN-E, and KETOPROFEN SR are 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

Patients with impaired hepatic function should be carefully monitored and kept at the minimal effective daily dosage. KETOPROFEN, KETOPROFEN-E, and KETOPROFEN SR are contraindicated in severe liver impairment or active liver disease. See 2 CONTRAINDICATIONS.

4.4 Administration

KETOPROFEN should be taken with meals to minimize gastrointestinal intolerance.

KETOPROFEN-E and KETOPROFEN SR should be taken 1 to 2 hours before meals or at least 2 hours after meals.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule. The patient should be instructed not to take 2 doses at the same time.

5 OVERDOSAGE

Symptoms

Cases of overdose have been reported with doses up to 2.5 g of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. In most instances, the symptoms have been limited to lethargy, drowsiness, nausea, vomiting and epigastric pain. Headache, rarely diarrhoea, disorientation, excitation, coma, dizziness, tinnitus, fainting, occasionally convulsions may also occur. Adverse effects seen after overdose with propionic acid derivatives such as hypotension, bronchospasm and gastro-intestinal haemorrhage should be anticipated.

In cases of significant poisoning, acute renal failure and liver damage are possible.

If renal failure is present, haemodialysis may be useful to remove circulating medicinal product.

Treatment

There are no specific antidotes to KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR overdosages. In cases of suspected massive overdosages, a gastric lavage is recommended, and symptomatic and supportive treatment should be instituted to compensate for dehydration, to monitor urinary excretion and to correct acidosis, if present.

Within one hour of ingestion, consideration should be given to administering activated charcoal in an attempt to reduce absorption of slowly-released ketoprofen.

Alternatively, in adults, gastric lavage, aimed at recovering pellets that may still be in the stomach, should be considered if the patient presents within 1 hour of ingesting a potentially toxic amount.

Correction of severe electrolyte abnormalities may need to be considered.

Renal and liver function should be closely monitored.

The drug is dialyzable; therefore, hemodialysis may be useful to remove circulating drug and to assist in case of renal failure.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 50 mg	Colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10, FD&C green #3, FD&C yellow #6, gelatin, lactose monohydrate, magnesium stearate, talc and titanium dioxide. The capsule is imprinted with edible red ink.
Oral	Enteric-coated tablets 50 mg, 100 mg	Colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10, dextrates, guar gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer dispersion, methylcellulose, polyethylene glycol, sunset yellow supra, talc, titanium dioxide and triethyl citrate.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	SR (Sustained-release) tablets 200 mg	Colloidal silicon dioxide, dextrates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polyvinyl acetate phthalate, stearic acid, titanium dioxide and triethyl citrate.

Description

KETOPROFEN 50 mg capsules are ivory opaque body, dark-green opaque cap, hard gelatin capsules, imprinted “50” with white powder fill. Available in bottles of 100, 500 and 1000.

KETOPROFEN-E 50 mg enteric-coated tablets are pale yellow, round, biconvex enteric-coated tablets, engraved “50” on one side, other side plain. Available in bottles of 100, 500 and 1000.

KETOPROFEN-E 100 mg tablets are pale yellow, round, biconvex, enteric-coated tablets, engraved “100” on one side, other side plain. Available in bottles of 100, 500 and 1000.

KETOPROFEN SR 200 mg tablets are white, round, biconvex, enteric-coated tablets, engraved “200” on one side, other side plain. Available in bottles of 100 and 500, and unit dose packages of 100 (10x10).

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.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are 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

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are non-steroidal anti-inflammatory drugs (NSAIDs). 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR should hypertension either develop or worsen with its use.

Use of NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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

Potential Effects on Driving and Using Machinery: Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. Therefore, patients should exercise caution in carrying out potentially hazardous activities that require alertness.

Endocrine and Metabolism

Corticosteroids: KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are NOT substitutes 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 peptic/duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Healthcare professionals should remain alert for ulceration and bleeding in patients treated with KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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. The incidence of these complications increases with increasing dose. **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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) including KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. Unlike most adverse reactions, which usually manifest themselves in the first month if they are going to occur in an individual, new peptic ulcers keep appearing in patients under treatment with KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR at a rate of greater than 1% per year.

Caution should be taken if prescribing KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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).

Patients taking KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 without warning symptoms or signs and at any time during the treatment.

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs, KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR should be discontinued, an appropriate treatment instituted 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR therapy when and if these adverse reactions appear.

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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are administered.

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

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 or AST occurred in controlled clinical trials in less than 1% of patients.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of 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 this drug as with other 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.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are contraindicated in patients with severe liver impairment or active liver disease. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests

Immune

Infection: KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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.

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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: KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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.

Monitoring and Laboratory Tests

The following testing or monitoring is recommended for various populations of patients taking KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. This is not an exhaustive list.

Cardiovascular: Blood pressure should be monitored regularly. 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR treatment. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

Ophthalmologic: An ophthalmologic examination should be carried out at periodic intervals. See 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.

Pregnancy: If KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR be closely monitored for amniotic fluid volume since KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR may result in reduction of amniotic fluid volume and even oligohydramnios. KETOPROFEN, KETOPROFEN-E and KETOPROFEN are 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR treatment. Electrolytes including serum potassium should be monitored. See 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Renal and 9 DRUG INTERACTIONS.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia with the use of NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR and other NSAIDs. If such symptoms develop KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR should be discontinued and an ophthalmologic examination performed. Ophthalmic examination should be carried out at periodic intervals in any patients receiving KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR.

Renal

Long-term administration of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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.

Ketoprofen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR should be anticipated and patients carefully monitored. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 10.3 Pharmacokinetics, Special Populations and Conditions.

Advanced Renal Disease: See 2 CONTRAINDICATIONS.

Fluid and Electrolyte Balance: Use of NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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.

Skin

Serious skin reactions*:* Use of some NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR, 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,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- 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

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are 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

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are contraindicated for use in breast feeding women. See 2 CONTRAINDICATIONS.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 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 as 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 nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal.

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.

In clinical trials of ketoprofen involving 1,542 patients, the most common side effects reported were gastrointestinal (22%). The most severe were peptic ulcer or GI bleeding which occurred in controlled clinical trials in less than 1% of 1,076 patients; however, in open label continuation studies in 1,292 patients the rate was greater than 2%.

Table - Adverse reactions reported with KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR

	Ketoprofen (%)
Cardiac disorders	peripheral edema (2%)

	Ketoprofen (%)
Gastrointestinal disorders (22%)	dyspepsia (12.8%) nausea (4.0%) indigestion and flatulence (2.8%) vomiting (2.0%) constipation (2.0%) diarrhea (1.4%)
Nervous system disorders (3-5%)	headache (1.7%) fatigue (1%)
Skin and subcutaneous reactions (<3%)	rashes (1.7%)

8.3 Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia.

Cardiac disorders: palpitation, congestive heart failure.

Ear and labyrinth disorders: tinnitus, hearing impairment.

Eye disorders: visual disturbance, conjunctivitis, conjunctivitis sicca.

Gastrointestinal disorders: ulcer, GI bleeding and perforation, melena, hematemesis, stomatitis, taste perversion.

Hepatobiliary disorders: hepatic dysfunction, jaundice.

Immune system disorders: anaphylaxis.

Metabolism and nutrition disorders: anorexia.

Nervous System disorders: dizziness, drowsiness, vertigo, migraine, paresthesia.

Psychiatric disorders: tension, anxiety, depression, impotence.

Skin and subcutaneous tissue disorders: angioedema, pruritus, flushing, excessive perspiration, alopecia, bullous rash, exfoliative dermatitis, photosensitivity, purpuric rash, urticaria, onycholysis.

Renal and urinary disorders: interstitial nephritis, hematuria, nephrotic syndrome, impairment of renal function, acute renal failure.

Respiratory, thoracic and mediastinal disorders: asthma, life threatening bronchospasm.

Vascular disorders: hypertension.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Laboratory Tests: Abnormal alkaline phosphatase, lactic dehydrogenase, glutamic oxaloacetic transaminase and blood urea nitrogen values were found in some patients receiving ketoprofen therapy. The abnormalities did not lead to discontinuation of treatment and, in some cases, returned to normal while the drug was continued. There have been sporadic reports of decreased hematocrit and hemoglobin values without progressive deterioration on prolonged administration of the drug.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

There are no specific studies about the 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. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal.

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 - Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic Acid (ASA) or other NSAIDs	T	Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.	The use of KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR in addition to any other NSAID, including over-the counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.
Antacids	T	Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with the rate or extent of the absorption of KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR.	

Common name	Source of Evidence	Effect	Clinical comment
Anti-hypertensives	T	NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia.	Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular
Anti-platelet Agents (including ASA)	T	There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. See 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-platelet Effects.	Monitor for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS, Hematologic
Cyclosporin	T	Increased risk of nephrotoxicity, particularly in elderly subjects.	Monitor for signs of worsening renal function. Monitor for dosage adjustment
Digoxin	T	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. A pharmacokinetic interaction between KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR and digoxin has not been demonstrated.	Caution is advised, in particular in patients with renal impairment, since NSAIDs may reduce renal function and decrease renal clearance of cardiac glycosides. Monitor serum digoxin levels

Common name	Source of Evidence	Effect	Clinical comment
Diuretics	C	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. Hydrochlorothiazide, given concomitantly with KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone.	Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. See 7 WARNINGS AND PRECAUTIONS
Glucocorticoids	CT	Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.	Monitor patients, particularly those over 65 years of age, for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS
Lithium	C	Nonsteroidal anti-inflammatory agents have been reported to increase steady-state plasma lithium levels. Ketoprofen is extensively (99%) protein bound to human serum albumin and may compete for binding sites with drugs such as lithium.	It is recommended that plasma lithium levels be monitored when KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR are co-administered with lithium.

Common name	Source of Evidence	Effect	Clinical comment
Methotrexate	CT	The concomitant administration of KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR and high-dose methotrexate has been associated with prolonged and marked enhancement of serum methotrexate levels resulting in severe methotrexate toxicity. There were no abnormalities in methotrexate kinetics or evidence of toxicity when KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR was given at least 12 hours after completion of high-dose methotrexate infusion.	KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR should not be used in patients receiving high dose methotrexate. The potential for severe toxicity should be kept in mind when prescribing KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR and low-dose methotrexate concurrently. KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR should not be administered within 12 hours of methotrexate infusion.
Oral anticoagulants	CT	KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR has been shown to depress platelet aggregation and it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. See 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-coagulants.	Close monitoring of patients is recommended when KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR are given concomitantly with anticoagulants.
Mifepristone	T	NSAIDs should not be used for 8 – 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.	

Common name	Source of Evidence	Effect	Clinical comment
Oral hypoglycemics	T	KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR are extensively (99%) protein bound to human serum albumin and may compete for binding sites with drugs such as oral hypoglycemic agents.	patients should be monitored.
Probenecid	C	Concurrent administration of probenecid increases both free and bound ketoprofen through reducing the plasma clearance of ketoprofen to about one-third as well as decreasing its protein binding.	KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR are not recommended in association with probenecid.
Selective Serotonin Reuptake Inhibitors (SSRIs)	T	Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).	Monitor for signs for bleeding.
Sulfonamides, phenytoin	T	KETOPROFEN, KETOPROFEN -E and KETOPROFEN SR are extensively (99%) protein bound to human serum albumin and may compete for binding sites with drugs such as sulfonamides, phenytoin.	Patients with such combination therapy should be monitored.
Tacrolimus	T	Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus, particularly in elderly subjects.	Monitor for necessary dosage adjustment. Monitor for signs of worsening renal function.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Clinical Laboratory Tests

The presence of ketoprofen and its metabolites in urine has been shown to interfere with certain tests which are used to detect albumin, bile salts, 17-ketosteroids or 17-hydroxycorticosteroids in urine and which rely upon acid precipitation as an end point or upon color reactions for carbonyl groups. No interference was seen in the tests for proteinuria using Albustix, Hema-Combistix or Labstix Reagent Strips.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR decreases platelet adhesion and aggregation. Therefore, it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ketoprofen is a NSAID that possesses anti-inflammatory, analgesic, and antipyretic properties. The anti-inflammatory action is not mediated through the pituitary-adrenal axis.

Its therapeutic effectiveness has been demonstrated by a reduction in joint swelling, pain and duration of morning stiffness, and by increased grip strength and an improvement in functional capacity.

Clinical trials in rheumatoid arthritis have shown that the anti-arthritic activity of ketoprofen 200 mg/day was similar to that of acetylsalicylic acid 3.6 g/day.

Ketoprofen 200 mg daily induced less gastrointestinal bleeding than acetylsalicylic acid 3.6 g daily.

The effectiveness of ketoprofen as a general purpose analgesic has been studied in standard pain models which have shown the effectiveness of doses of 25 to 150 mg. Doses of 25 mg were superior to placebo. Larger doses than 25 mg generally could not be shown significantly more effective but there was a tendency toward faster onset and greater duration of action with 50 mg and, in the case of dysmenorrhea, a significantly greater effect overall with 75 mg. Doses greater than 50 to 75 mg did not have increased analgesic effect.

10.3 Pharmacokinetics

In man, ketoprofen is rapidly and almost completely absorbed from the gastrointestinal tract. Maximum plasma levels are reached within 1/2 to 2 hours after administration of capsules;

however, peak plasma levels are delayed by a further 1 to 2 hours with enteric-coated tablets and by 5 to 6 hours with sustained-release tablets. The biotransformation of ketoprofen is characterized by two main processes: hydroxylation and conjugation, the latter being the main metabolic pathway in man.

The drug is 99% bound to plasma proteins, mainly to the albumin fraction. Metabolites as well as the unchanged drug are excreted mainly in the urine. Fecal excretion is negligible.

Following the administration of capsules or enteric-coated tablets in man, 25% to 90% of the drug is excreted in the urine within 24 hours, with the major portion being excreted during the first 6 hours. The elimination half-life is approximately 2 hours. Following administration of slow release ketoprofen, absorption is gradual, reaching a plateau during which plasma levels remain steady from the fifth to the twelfth hour after ingestion and decrease with an apparent half-life of 3 to 4 hours. No accumulation of ketoprofen was found following repeated once-daily administration of ketoprofen sustained-release tablets. Repeated administration of the drug in man caused no induction of liver enzymes.

When ketoprofen capsules are administered with food, the total bioavailability (AUC) is not altered; however, the rate of absorption is slowed resulting in delayed and reduced peak concentrations (C_{max}). Following a single 50 mg dose of ketoprofen while fasting, the mean C_{max} was 4.1 mg/L (at 1.1 hours); when administered after food, it decreased to 2.4 mg/L (at 2.0 hours).

The composition of the diet slightly but significantly alters the extent of absorption of ketoprofen from sustained-release tablets: a high-fat/high calorie meal (3000 calories/day) was associated with lower ketoprofen bioavailability values (about 20%) than a low-fat/ low-calorie content (1200 calories/day). Mean trough ketoprofen plasma concentrations were similar after high or low fat meals.

Absorption

Ketoprofen is almost completely absorbed whether administered orally as capsules, enteric-coated or sustained-release tablets. Absorption is rapid after administration of the drug as an oral capsule with peak plasma concentrations occurring between 0.5 to 2 hours. Peak plasma levels are delayed by a further 1 to 2 hours with the enteric-coated tablets and by 5 to 6 hours with the sustained-release tablets. Food slows the rate of absorption of ketoprofen with the capsule formulation, resulting in delayed and reduced peak plasma concentrations, but the extent of absorption is not affected. Following single 50 mg capsule doses, the mean C_{max} of 4.1 mg/L occurs after about 1 hour in the fasted state compared with 2.4 mg/L after 2 hours in the non-fasted state. Concomitant administration of an aluminum and magnesium hydroxide antacid or an aluminum phosphate antacid does not appear to affect absorption of the drug.

The composition of the diet slightly but significantly alters the extent of absorption of ketoprofen from sustained-release tablets: a high-fat/high-calorie meal (approximately 3000 calories/day) was associated with lower ketoprofen bioavailability values (about 20%) than a low-fat/low-calorie content (approximately 1200 calories/day). Mean trough ketoprofen plasma concentrations were similar after high or low fat meals.

The area under the plasma concentration time curve (AUC) is linearly related to dose over the range of 75-200 mg and neither accumulation nor induction of liver enzymes occur after repeated doses. There is considerable inter-individual and intra-individual variation in plasma concentrations attained with a given dosage. Although the relationship between plasma ketoprofen concentrations and therapeutic effect has not been precisely determined, a therapeutic range of 0.4-6 mg/L has been suggested.

Distribution:

Like other NSAIDs, ketoprofen is highly (≅99%) protein bound. The apparent volume of distribution (Vd) is approximately 0.1 L/kg. The drug efficiently penetrates inflamed synovial fluid where peak concentrations are about 30% of those in plasma; by 4-6 hours after administration, synovial fluid concentrations exceed those in plasma.

Metabolism:

Ketoprofen is rapidly and extensively metabolized in the liver, principally by hydroxylation and conjugation; the latter being the main metabolic pathway in man. Metabolites as well as the unchanged drug are excreted mainly in the urine; fecal excretion is negligible.

Following the administration of capsules or enteric-coated tablets, 25% to 90% of the drug is excreted in the urine within 24 hours, with the major portion being excreted during the first 6 hours.

Elimination

In healthy volunteers, the apparent plasma clearance of ketoprofen averages approximately 1 to 1.3 mL/min/kg and the elimination half-life is approximately 2 hours.

Total apparent plasma clearance of the drug is decreased in patients with reduced renal function. In a group of patients with creatinine clearance of 20 to 60 mL/min., total apparent plasma clearance averaged 0.7 mL/min/kg. Total apparent plasma clearance is also similarly decreased in geriatric individuals, resulting in an increase in elimination half-life (2.7 hours vs. 1.77 hours in younger population).

Special Populations and Conditions

- **Geriatrics:** To date, studies of the effects of age and renal function impairment have been small, generally involving 5 to 8 subjects per group, but they indicate modest decrease in clearance in the elderly and in patients with impaired renal function. In normal elderly volunteers (mean age 73 years), the plasma and renal clearance and protein binding were reduced while the V_d increased when compared to a younger normal population (mean age 27 years). (Plasma clearance and V_d were 0.05 L/kg/hr and 0.4 L/kg in elderly and 0.06 L/kg/hr and 0.3 L/kg in young subjects, respectively). The mean half-life of ketoprofen in this normal geriatric population, as well as in a rheumatoid elderly population (mean age 64 years), was about 5 hours as compared to 3 hours in the younger population.
- **Renal Insufficiency:** Patients with impaired renal function (mean age 44 years) also demonstrate decreases in plasma clearance (0.04 L/kg/hr) of drug, with the mean

half-life increasing to about 3.5 hours.

11 STORAGE, STABILITY AND DISPOSAL

Store at a controlled room temperature 15-30°C. Protect unit dose packages from light.

KETOPROFEN should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None

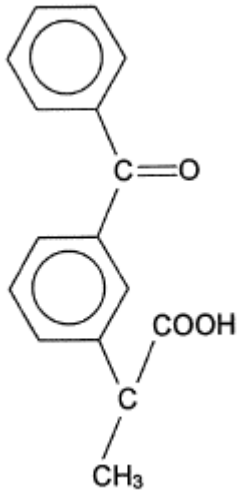
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	ketoprofen
Chemical name:	m-benzoylhydratropic acid
Molecular formula and molecular mass:	$C_{16}H_{14}O_3$ and 254.3 g/mol

Structural formula:



Physiochemical Properties: Ketoprofen is a white, odourless, non-hygroscopic, crystalline powder. Its melting point is approximately 93ºC. It is very soluble in ether, ethanol, chloroform, and acetone; soluble in benzene and slightly soluble in water.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

Bioavailability studies were performed using normal human volunteers. The rate and extent of absorption of ketoprofen after a single oral 50 mg dose of ORUDIS® 50 mg and KETOPROFEN 50 mg capsules were measured and compared. The results are summarized as follows:

	ORUDIS® 50 mg		KETOPROFEN 50 mg		% Diffr.
AUC_{0-12} (mcg. hr/mL)	9.93		9.49		-4.4
C_{max} (mcg/mL)	5.31		4.39		-17.3
T_{max} (hr)	1.12		1.35		+20.4
$t_{1/2}$ (hr)	1.7		1.6		-5.9

The rate and extent of absorption of ketoprofen after a single oral 50 mg dose of ORUDIS® E 50 mg and KETOPROFEN-E 50 mg enteric-coated tablets were measured and compared. The results are summarized as follows:

	ORUDIS® E 50 mg		KETOPROFEN-E 50 mg		% Diffr.
AUC_{0-12} (mcg. hr/mL)	9.59		9.72		+1.4
C_{max} (mcg/mL)	6.09		4.41		-27.7
T_{max} (hr)	1.5		1.6		+10.6
$t_{1/2}$ (hr)	1.8		1.8		0.0

Two additional bioavailability studies were performed using sustained-release tablets, one with food and one without food. The rate and extent of absorption of ketoprofen after a single oral 200 mg dose of ORUDIS® SR 200 mg and KETOPROFEN SR 200 mg tablets were measured and compared. The results from measured data are summarized as follows:

(Without Food)

Geometric Mean Arithmetic Mean (CV%)			
Parameter	KETOPROFEN SR	Orudis® SR†	Ratio of Means (%)
AUC_T (mcg.hr/mL)	30.3 31.0 (19)	31.2 31.7 (19)	96.9*
AUC_I (mcg.hr/mL)	34.5 35.1 (19)	35.5 36.1 (21)	97.1*
AUC_x (mcg.hr/mL)	30.3 31.9 (19)	31.2 31.6 (19)	97.2*
C_{max} (mcg/mL)	3.32 3.45 (32)	3.29 3.39 (28)	99.7*
T_{max} (hr)	10.2 (37)	7.08 (45)	-
$t_{1/2}$ (hr)	2.93 (23)	3.87 (53)	-
The T_{max} and $t_{1/2}$ parameters are expressed as the arithmetic means. † Orudis® SR (Rhône-Poulenc Rorer) was purchased at a Canadian retail pharmacy. *Based on the least squares estimate of the geometric means.			

Study 2 (With Food)

Geometric Mean Arithmetic Mean (CV%)			
Parameter	KETOPROFEN SR	Orudis® SR†	Ratio of Means (%)
AUC_T (mcg.hr/mL)	26.6 29.5 (44)	26.0 28.7 (45)	98.4*
AUC_I (mcg.hr/mL)	30.6 33.5 (39)	29.4 32.2 (42)	97.6*

Geometric Mean Arithmetic Mean (CV%)			
Parameter	KETOPROFEN SR	Orudis® SR†	Ratio of Means (%)
AUC_x (mcg.hr/mL)	25.3 27.9 (43)	24.3 26.3 (39)	101.8*
C_{max} (mcg/mL)	3.46 3.53 (20)	3.94 4.14 (29)	82.2*
T_{max} (hr)	11.9 (39)	9.69 (61)	-
$t_{1/2}$ (hr)	3.13 (53)	2.15 (41)	-
The T_{max} and $t_{1/2}$ parameters are expressed as the arithmetic means. † Orudis® SR (Rhône-Poulenc Rorer) was purchased at a Canadian retail pharmacy. *Based on the least squares estimate of the geometric means.			

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

LD_{50} (and 95% probability level exclusive of the 20% confidence limits) mg/kg.

Species	Sex	Oral
Mice *	F	320 (209.0-490.0)
	M	198 (150.0-261.0)
	Combined	221 (187.0-261.1)
Rats **	F	109 (84-141)
	M	109 (84-141)
	Combined	109 (91-131)

* 12 groups, each with 5 animals/sex were treated with the test article (ketoprofen) at logarithmically spaced doses.

** 9 groups, each with 5 animals/sex were treated with the test article (ketoprofen) at logarithmically spaced doses.

Mortality generally occurred within a 6 day period post-dosing in mice, and over a 12 day period in rats.

In mice, pharmacotoxicity was generally characterized by decreased activity, muscle tone and reflexes, ataxia, piloerection, hunchback, and paleness or cyanosis.

In rats, pharmacotoxicity was generally characterized by piloerection, ptosis, paleness, emaciation, epistaxis, decreased activity and reflexes, cyanosis, hunchback, diarrhea, decreased muscle tone, ataxia, and coma.

Necropsy of animals succumbing during the study generally demonstrated pale or dark liver, mild to severe irritation and/or hemorrhage of the small intestine, distended small intestine, pale stomach with severe irritation or hemorrhage, distended stomach, pale or dark spleen and pale or dark kidneys.

Animals sacrificed upon completion of the study showed no pathological findings in mice but red ascites, distention of the stomach and apparent enlargement of the spleen were seen in rats.

Subacute Toxicity

The subacute oral LD_{50} for ketoprofen in the mouse and rat was 180 mg/kg/day and 21 mg/kg/day, respectively, based on treatment for 5 consecutive days.

Chronic Toxicity

Rat

Ketoprofen was administered orally to rats at doses ranging from 2 to 36 mg/kg/day for 1 month, 6 to 24 mg/kg/day for 3 months and 4.5 to 12.5 mg/kg/day for 18 months.

The main pathological findings were gastrointestinal irritation and ulceration, the severity of which was related to the dose administered and to the length of exposure. These changes occurred with doses of 7.5 mg/kg/day and above.

At doses of 18 mg/kg/day p.o. for one month and 12 mg/kg/day p.o. for 3 months, changes in the gastric mucosa were less severe while doses of 27 and 36 mg/kg/day for one month, 24 mg/kg/day for 3 months and 7.5 and 12.5 mg/kg/day for 18 months produced serious gastric ulceration leading to an increased mortality incidence. On chronic oral administration, nephropathy was observed at all doses. The changes involved both cortex and papilla and were extensive at higher doses.

Dog

In the dog, daily oral doses of 2, 6, 18, and 36 mg/kg for 1 month and 3, 6, 12, and 24 mg/kg for 3 months were administered. At doses of 3, 6 and 12 mg/kg for 3 months, gastric ulcerations were revealed at autopsy. At daily doses of 18 and 36 mg/kg for 1 month and of 24 mg/kg for 3 months, there was weight loss, severe dose-related gastric ulceration, anemia with occasional hyperleukocytosis, and, in a few males, testicular involution; laboratory determinations revealed, in some animals, decreases in serum total protein content and albumin/globulin ratio, hyperfibrinemia and an increase of the erythrocyte sedimentation rate.

Baboon

Ketoprofen was administered at oral doses of 4.5, 9 and 27 mg/kg/day for one year. Two control groups received either lactose or indomethacin 4.5 mg/kg/day.

No abnormal clinical signs were recorded with either ketoprofen or indomethacin. There was temporary suppression of weight gain during the first 6 weeks in animals receiving 27 mg/kg of ketoprofen.

Post-mortem examination revealed a variety of minor changes in the gastrointestinal tract which in the main consisted of areas of congestion, small depressions and minimal erosions. These were present in all test groups, including the control groups.

Two out of 12 animals receiving 27 mg/kg, the first sacrificed after 26 weeks, the second after one year, showed an area of scarring in the pyloric antrum which suggested a healed ulcer.

Carcinogenicity:

The carcinogenic potential of ketoprofen was studied in C_{57}B1/6/Rho-Ico mice. The drug was administered in drinking water at dosages of 2, 4, 8, 16 and 32 mg/kg/day for 105 weeks.

Tumours observed in control and treated groups showed no pattern indicative of carcinogenicity. There was a dose-related incidence of endometrial hyperplasia.

Ketoprofen did not show mutagenic potential in the Ames Test.

Ulcerogenic Activity

In fasting rats, ketoprofen, at dosages of 4 and 8 mg/kg p.o. for 4 days was comparable in terms of ulcerogenic activity to indomethacin 2 and 4 mg/kg p.o. Ketoprofen 1 and 2 mg/kg p.o. had no effect on the gastrointestinal mucosa.

Reproductive and Developmental Toxicology:

In the rat, ketoprofen was administered orally at dosages of 3, 6 and 9 mg/kg daily. In males, the drug was administered during 11 consecutive weeks, mating with untreated females taking place during the last week of dosing. In females, ketoprofen was administered during the two weeks which preceded mating with untreated males, the mating period and the two first weeks of gestation.

At 9 mg/kg, 4 out of 17 males and 2 out of 36 females died with definite signs of gastrointestinal damage. However, with the exception of a slightly decreased implantation rate observed in females receiving the two higher dosages (not dose related), ketoprofen exerted no effects on fertility and on the general reproductive functions of male and female rats.

Teratogenicity studies with ketoprofen were conducted in mice, rats and rabbits, using the following dosage schedules.

Mice: 3, 6, and 9 mg/kg p.o. from day 5 to 15 of pregnancy.

Rats: 3, 6, and 9 mg/kg p.o. from day 5 to 15 of pregnancy.

Rabbits: 2, 3, 4, 6 and 12 mg/kg p.o. from day 6 to 16 of pregnancy.

In these studies, there was no evidence of drug induced teratogenic activity.

Female rats were given oral ketoprofen 3, 6 and 9 mg/kg from day 15 of gestation through lactation, to 21 days post-partum. Rats receiving indomethacin 1.5, 3 and 6 mg/kg were used as controls.

Both drugs exerted an inhibitory effect on the ultimate stage of pregnancy and on parturition; a large number of animals treated at the intermediate and high dosage levels died either just before, during or shortly after parturition with evidence of dystocia. The maximum tolerated dosage was about 3 mg/kg per day. At this level, litter parameters from birth through lactation to weaning appeared unaffected by treatment. No malformations were observed among the young born to treated mothers.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrKETOPROFEN, PrKETOPROFEN-E and PrKETOPROFEN SR
Ketoprofen Capsules BP, Ketoprofen Enteric-coated Tablets and Ketoprofen Sustained-release Tablets

Read this carefully before you start taking **KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR** 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 **KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR 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:

- KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Pregnancy:

- **DO NOT** take KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR if you are told to do so by your healthcare professional.
- Medicines like KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR.

What is KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR used for?

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR are used in adults and children 12 years and older to:

- Treat the signs and symptoms of arthritis disorders such as:
    - Osteoarthritis
    - Rheumatoid arthritis
- Treat period cramps (primary dysmenorrhea).
- Help relieve mild to moderate pain:
    - with inflammation in sprains and strains
    - after surgery (including dental surgery)
    - after giving birth (postpartum pain)

Your healthcare professional should consider other treatments first if you are at higher risk of having heart, stomach or intestine problems.

How does KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR work?

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR belong to group of medicines called nonsteroidal anti-inflammatory drug (NSAIDs). It can reduce the chemicals produced by your body which cause pain and swelling.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR do NOT cure your illness or prevent it from getting worse. It can only treats the symptoms and relieves pain and inflammation as long as you take it.

What are the ingredients in KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR?

Medicinal ingredients: Ketoprofen

Non-medicinal ingredients:

KETOPROFEN: Colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10, FD&C green #3, FD&C yellow #6, gelatin, lactose monohydrate, magnesium stearate, talc, titanium dioxide. The capsule is imprinted with edible red ink.

KETOPROFEN-E: Colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10, dextrates, guar gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer dispersion, methylcellulose, polyethylene glycol, sunset yellow supra, talc, titanium dioxide and triethyl citrate.

KETOPROFEN SR: Colloidal silicon dioxide, dextrates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polyvinyl acetate phthalate, stearic acid, titanium dioxide and triethyl citrate.

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR come in the following dosage forms:

- KETOPROFEN: Capsule, 50 mg
- KETOPROFEN-E: Enteric coated Tablet, 50 mg and 100 mg

- KETOPROFEN SR: Sustained-release Tablet, 200 mg

Do not use KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR if you:

- have heart bypass surgery (planning to have or recently had).
- have severe, uncontrolled heart failure.
- have 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 ketoprofen or any other ingredients in the formulation 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 intestinal 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 (moderate, severe or worsening).
- have high potassium in the blood.
- are under 12 years old.
- have lactose intolerance.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR. 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 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR
- have immune system problems
- are taking other NSAID products including low-dose ASA or aspirin
- are on a low-salt diet

Other warnings you should know about:

Serious Side Effects: KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR may cause serious side effects, including:

- **Blood and bleeding problems**:
  - KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR can cause blood problems, bleeding and prolonged bleeding.
  - Taking KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR with the following medicines 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 or life-threatening skin reactions listed below have been reported with some NSAIDs, such as KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR. 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.

  KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR to monitor your health. They will:

- Check your blood pressure.
- Check your eyes. KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 machinery: KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR, do NOT drive or operate machinery.

Fertility in Women: KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR. 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR. 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 KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR:

- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever, or inflammation, like:
    - celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- 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
- Corticosteroids (including glucocorticoids), used to treat inflammation, like prednisone
- Medicines used to treat diabetes
- Medicines used to treat bacteria infections (antibiotics), like sulphonamides
- Medicines used to lower the risk of organ transplant rejection, like cyclosporine and tacrolimus
- Digoxin, used to treat heart disorders
- Medicines used to treat different cancers, like methotrexate
- Mifepristone, used for abortions. KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR should not be taken for 8-12 days after taking mifepristone.
- Probenecid, used to treat gout
- Phenytoin, used to treat seizures
- Alcohol

How to take KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR:

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR:

- Take exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- If you will be taking this medicine for more than 7 days, see your health care professional regularly. They will check if it is working for you and if it is causing you any side effects.

- **This medication 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.**

KETOPROFEN:

- Take right after a meal or with food to avoid an upset stomach.

KETOPROFEN-E, KETOPROFEN SR:

- Take 1 to 2 hours before meals or at least 2 hours after meals.
- Swallow your tablets whole. Do not break, crush, or chew them.

Usual dose:

KETOPROFEN, KETOPROFEN-E and KETOPROFEN SR:
Adults and Children 12 years and older:

- Your healthcare professional will decide on the best dosage for you based on your condition.
- Your healthcare professional may change 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR, 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, 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 KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR?

These are not all the possible side effects you may have when taking KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR. 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
- Loss of appetite
- Taste disorder, thirst, dry mouth

- Mouth sores/swelling
- Weight gain
- Eating disorder
- Headache, dizziness, lightheadedness
- Feeling of burning/prickliness/numbing
- Confusion, depression, anxiety, tension
- Hearing problems.
- Bruises, skin rash, swelling, hives or itching
- Hair loss
- Increased sweating
- Stiff neck
- Muscle pain

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**	
VERY 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		✓	
COMMON			
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		✓	

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	
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): 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,		✓	

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**	
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 a controlled room temperature (15-30°C). Protect from light.

Ask your healthcare professional on how to dispose of medicines you no longer use. Do not throw away in your household garbage.

Keep out of reach and sight of children.

If you want more information about KETOPROFEN, KETOPROFEN-E or KETOPROFEN SR:

- 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 (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA PHARMA INC.

Last Revised: MAY 10, 2022