PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MINT-KETOROLAC

Ketorolac Tromethamine Tablets

Tablets, 10 mg, For Oral Use

House Standard

Non-Steroidal Anti-Inflammatory Drug (NSAID)

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Gastrointestinal	03/2025

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Certain sections (as indicated in section 2.1. of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MINT-KETOROLAC (ketorolac tromethamine tablets) is indicated for:

- Short-term management (not to exceed 5 days for post-surgical patients or 7 days for patients with musculoskeletal pain) of moderate to moderately severe acute pain, including post-surgical pain (such as general, orthopedic and dental surgery), acute musculoskeletal trauma pain and post-partum uterine cramping pain. See 7 WARNINGS AND PRECAUTIONS, General and 4.2 Recommended Dose and Dosage Adjustment.

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 and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Gastrointestinal.

Use of MINT-KETOROLAC 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, Cardiovascular, Gastrointestinal.

MINT-KETOROLAC, as a NSAID, does NOT treat clinical disease or prevent its progression.

MINT-KETOROLAC, 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): MINT-KETOROLAC is contraindicated in the pediatric population. 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 7.1.4 Geriatrics and 4.2 Recommended Dose and Dosage Adjustment.

2 CONTRAINDICATIONS

MINT-KETOROLAC is contraindicated in:

- Patients who are hypersensitive to MINT-KETOROLAC 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 ketorolac tromethamine 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.

- During the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition.
- Labour and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.
- 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, Immune.
- Active gastric / duodenal / peptic ulcer, active GI bleeding.
- Inflammatory bowel disease.
- Cerebrovascular bleeding or other bleeding disorders.
- Coagulation disorders, post-operative patients with high hemorrhagic risk or incomplete hemostasis in patients with suspected or confirmed cerebrovascular bleeding.
- Immediately before any major surgery and intraoperatively when hemostasis is critical because of the increased risk of bleeding.
- Severe liver impairment or active liver disease.
- Moderate to severe renal impairment (serum creatinine >442 micromol/L and/or 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.
- Concurrent use with other NSAIDs due to the absence of any evidence demonstrating synergistic benefits and potential for additive side effects. See 9.1 Serious Drug Interactions.
- Concomitant use with probenecid. See 9.1 Serious Drug Interactions.
- Concomitant use with pentoxifylline. See 9.1 Serious Drug Interactions.
- Children and adolescents aged less than 18 years.

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

  MINT-KETOROLAC 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 MINT-KETOROLAC 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 MINT-KETOROLAC, 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 ketorolac tromethamine have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing MINT-KETOROLAC.

- **Risk of Gastrointestinal (GI) Adverse Events:** See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal

  Use of NSAIDs, such as MINT-KETOROLAC, 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 MINT-KETOROLAC 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 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pregnancy). MINT-KETOROLAC is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition). See 2 CONTRAINDICATIONS.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Use of MINT-KETOROLAC should be limited to the lowest effective dose for the shortest possible duration of treatment. See 1 INDICATIONS.

In no case is the duration of MINT-KETOROLAC treatment to exceed 7 days.

Conversion from Parenteral to Oral Therapy

When MINT-KETOROLAC tablets are used as a follow-on therapy to parenteral ketorolac, the total combined daily dose of ketorolac (oral + parenteral) should not exceed 120 mg in younger adult patients or 60 mg in elderly patients on the day the change of formulation is made. On subsequent days, oral dosing should not exceed the recommended daily maximum of 40 mg. Ketorolac (parenteral) should be replaced by an oral analgesic as soon as feasible.

The total combined duration of intramuscular and oral treatment should not exceed 5 days.

4.2 Recommended Dose and Dosage Adjustment

Adults (>18 years of age)

Dosage should be adjusted according to the severity of the pain and the response of the patient.

The usual oral dose of MINT-KETOROLAC (ketorolac tromethamine) is 10 mg every 4 to 6 hours for pain as required. Doses exceeding 40 mg per day are not recommended. The maximum duration of treatment with the oral formulation is 5 days for post-surgical patients and 7 days for patients with musculoskeletal pain. MINT-KETOROLAC is not indicated for chronic use.

Renal Impairment

MINT-KETOROLAC is contraindicated in patients with moderate to severe renal impairment (serum creatinine >442 micromol/L). MINT-KETOROLAC should be used with caution in patients with lesser renal impairment (serum creatinine 170 - 442 micromol/L). Such patients should receive a reduced dose of MINT-KETOROLAC, and their renal status should be closely monitored. It is recommended that the daily dose be reduced by half; a total daily dose of 20 mg should not be exceeded. On the day of conversion from parenteral ketorolac tromethamine to Mint-Ketorolac tablets, the total combined ketorolac tromethamine dose (oral + parenteral) should not exceed 60 mg. Dialysis does not significantly clear ketorolac from bloodstream. See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Renal, 10.3 Pharmacokinetics.

Hepatic Impairment

MINT-KETOROLAC is contraindicated in patients with severe liver impairment or active liver disease.

Caution should be observed in giving MINT-KETOROLAC to patient with mild to moderate hepatic insufficiency. See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS,

Hepatic/Biliary/Pancreatic, 10.3 Pharmacokinetics.

Elderly, Frail or Debilitated Patients

These patients are at increased risk of the serious consequences of adverse reactions.

The lowest effective dose is recommended. See 7.1.4 Geriatrics.

4.4 Administration

MINT-KETOROLAC should be taken with meals to minimize gastrointestinal intolerance.

4.5 Missed Dose

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

5 OVERDOSAGE

Signs and Symptoms

Overdoses of ketorolac tromethamine have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis, gastrointestinal bleeding, and renal dysfunction which have generally resolved after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage. Although rare, hypertension, acute renal failure, respiratory depression, coma and death have been reported after significant overdose of NSAIDs. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

In a gastroscopic study of healthy subjects, daily doses of 360 mg given over an 8-hour interval for each of five consecutive days (3 times the highest recommended dose) caused pain and peptic ulcers which resolved after discontinuation of dosing

Treatment

Patients should be managed by symptomatic and supportive care following overdose. There are no specific antidotes. Dialysis does not significantly clear ketorolac from the bloodstream.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

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	tablet 10 mg of ketorolac tromethamine	Hypromellose, lactose monohydrate, macrogol 4000, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

MINT-KETOROLAC (ketorolac tromethamine) is available as 10 mg white round biconvex film coated tablets. MINT-KETOROLAC 10 mg tablet is available in bottles of 100.

MINT-KETOROLAC Tablets

Each MINT-KETOROLAC 10 mg tablet contains ketorolac tromethamine, the active ingredient, with microcrystalline cellulose, lactose monohydrate and magnesium stearate. The coating suspension contains hypromellose, titanium dioxide and macrogol 4000.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

The long-term use of MINT-KETOROLAC (ketorolac tromethamine) is not recommended as the incidence of side-effects increases with the duration of treatment. See 1 INDICATIONS and 4 DOSAGE AND ADMINISTRATION.

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.

MINT-KETOROLAC 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

MINT-KETOROLAC 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 MINT-KETOROLAC 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 MINT-KETOROLAC, 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 MINT-KETOROLAC should hypertension either develop or worsen with its use.

Use of NSAIDs, such as MINT-KETOROLAC, 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 MINT-KETOROLAC. Therefore, patients should exercise caution in carrying out potentially hazardous activities that require alertness.

Endocrine and Metabolism

Corticosteroids

MINT-KETOROLAC (ketorolac tromethamine) 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

GI Ulceration, Bleeding and Perforation

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

Caution should be taken if prescribing MINT-KETOROLAC 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)

Close medical supervision is recommended in patients prone to gastrointestinal tract irritation. In these cases, the physician must weigh the benefits of treatment against the possible hazards.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of therapy with ketorolac tromethamine when and if these adverse reactions appear.

Anastomotic Leak

NSAIDs, including ketorolac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using MINT-KETOROLAC after gastrointestinal surgery.

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 an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with MINT-KETOROLAC **must be stopped immediately** to obtain recovery. 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 hemophilia or platelet disorders should be carefully observed when MINT-KETOROLAC is administered.

Anti-coagulants

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

Even with therapeutic INR monitoring, increased bleeding may occur.

Use of MINT-KETOROLAC in patients who are receiving therapy that affects hemostasis should be undertaken with caution, including close monitoring. The concurrent use of ketorolac tromethamine and prophylactic, low dose heparin (2500 to 5000 units q12h), warfarin and dextrans may also be associated with an increased risk of bleeding.

Prothrombin time should be carefully monitored in all patients receiving oral anticoagulant therapy concomitantly with ketorolac tromethamine.

The *in vitro* binding of warfarin to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs. 99.3%) at plasma concentrations of 5 to 10 mcg/mL

Anti-platelet Effects

Ketorolac tromethamine inhibits platelet function and may prolong bleeding time. It does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT).

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. The inhibition of platelet function by ketorolac tromethamine is normalized within 24 to 48 hours after the drug is discontinued.

Ketorolac tromethamine 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 MINT-KETOROLAC 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 ketorolac tromethamine. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on treatment with MINT-KETOROLAC 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 elevations (greater than 3 times normal) of serum transaminases (glutamate pyruvate [SGPT or ALT] and glutamic oxaloacetic [SGOT or AST]), occurred in clinical trials in less than 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.), ketorolac tromethamine should be discontinued.

MINT-KETOROLAC is 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. Caution should be observed if MINT-KETOROLAC is to be used in patients with a history of liver disease. Patients with impaired hepatic function from

cirrhosis do not have any clinically important changes in ketorolac tromethamine clearance. See 2 CONTRAINDICATIONS and 10.3 Pharmacokinetics, Special Populations and Conditions.

Studies in patients with active hepatitis or cholestasis have not been performed.

Immune

Infection

MINT-KETOROLAC, 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 healthcare 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 ketorolac tromethamine. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving ketorolac tromethamine. MINT-KETOROLAC 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

MINT-KETOROLAC 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 MINT-KETOROLAC. This is not an exhaustive list.

Cardiovascular

Blood pressure should be monitored (in case of concomitant anti- hypertensives, and in susceptible patients with fluid retention). See 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG

INTERACTIONS.

Hematology

Concurrent therapy with anticoagulants require close monitoring of the international normalized ratio (INR). Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets may require monitoring. 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. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

Ophthalmologic

An ophthalmologic examination may be required. See 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.

Pregnancy

If MINT-KETOROLAC is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on MINT-KETOROLAC be closely monitored for amniotic fluid volume since MINT-KETOROLAC may result in reduction of amniotic fluid volume and even oligohydramnios. MINT-KETOROLAC 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 case of co-prescription of anti-hypertensives, methotrexate, cyclosporine, adrenergic blockers and in susceptible patients regarding the renal effects of NSAIDS e.g. impaired renal function or dehydration). 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 with the use of NSAIDs, such as MINT-KETOROLAC. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop, MINT-KETOROLAC should be discontinued and an ophthalmologic examination performed.

Ophthalmologic examination should be carried out at periodic intervals in any patient receiving NSAIDs for an extended period of time.

Peri-Operative Considerations

See 2 CONTRAINDICATIONS.

Psychiatric

Some patients may experience depression and insomnia with the use of NSAIDs, such as MINT-KETOROLAC.

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 renal failure, acute interstitial nephritis, renal papillary necrosis, 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, sepsis 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 MINT-KETOROLAC, 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.

Elevations of blood urea nitrogen (BUN) and creatinine have been reported in clinical trials with ketorolac. MINT-KETOROLAC is CONTRAINDICATED in patients with moderate to severe renal impairment.

Advanced Renal Disease

See 2 CONTRAINDICATIONS.

Fluid and Electrolyte Balance

Use of NSAIDs, such as MINT-KETOROLAC, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure, edema, and exacerbation of congestive heart failure. NaCl retention, oliguria, elevations of serum urea nitrogen and creatinine have also been observed in patients treated

with ketorolac tromethamine. Thus, caution should be exercised in prescribing MINT-KETOROLAC in patients with a history of congestive heart failure, compromised cardiac function, cardiac decompensation, hypertension, increased age or other conditions predisposing to fluid retention. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

Use of NSAIDs, such as MINT-KETOROLAC, 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 MINT-KETOROLAC, 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 MINT-KETOROLAC 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 MINT-KETOROLAC, 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

MINT-KETOROLAC 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 MINT-KETOROLAC 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 MINT-KETOROLAC 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 the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased

incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

MINT-KETOROLAC is contraindicated 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

MINT-KETOROLAC is contraindicated in women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants. See 2 CONTRAINDICATIONS.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): MINT-KETOROLAC is contraindicated for use in pediatric patients. 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.

Post-marketing experience with ketorolac tromethamine suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding, and perforation in the elderly and most spontaneous reports of fatal gastrointestinal events are in this population. Because ketorolac is cleared somewhat more slowly by the elderly (see 10.3 Pharmacokinetics), extra caution is recommended and the lowest effective dose should be used. See 4.1 Dosing Considerations and 4.2 Recommended Dose and Dose Adjustment.

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.

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.

KETOROLAC TROMETHAMINE TABLETS

SHORT-TERM PATIENT STUDIES

The incidence of adverse reactions in 371 patients receiving multiple 10 mg doses of ketorolac tromethamine for pain resulting from surgery or dental extraction during the post- operative period (less than 2 weeks) is listed below. These reactions may or may not be drug- related.

Table 2 Most Common Clinical Trial Adverse Drug Reactions (4 to 9% and 2 to 3%)

Body System	Incidence	Adverse Reaction
Gastrointestinal disorders	4-9%	Nausea
	2-3%	Diarrhea, dyspepsia, gastrointestinal pain, constipation
General disorders and administration site conditions	2-3%	Fever
Nervous system disorders	4-9%	Somnolence, insomnia
	2-3%	Nervousness, headache, dizziness

LONG-TERM PATIENT STUDY

The adverse reactions listed below were reported to be probably related to study drug in 553 patients receiving long-term oral therapy (approximately 1 year) with ketorolac tromethamine.

Table 3 - Most Common Clinical Trial Adverse Drug Reactions (10 to 12%, 4 to 9% and 2 to 3%)

Body System	Incidence	Adverse Reaction
Gastrointestinal disorders	10-12%	Dyspepsia, gastrointestinal pain
	4-9%	Nausea, constipation
	2-3%	Diarrhea, flatulence, gastrointestinal fullness, peptic ulcers

Metabolism and nutrition disorders		
	2-3%	Edema
Nervous system disorders	4-9%	Headache
	2-3%	Dizziness, somnolence

8.3 Less Common Clinical Trial Adverse Reactions

KETOROLAC TROMETHAMINE TABLETS

SHORT-TERM PATIENT STUDIES

Table 4 - Less Common Clinical Trial Adverse Drug Reactions (≤ 1%)

Body System	Adverse Reaction
Ear disorders	Ear pain
Eye disorders	Abnormal vision, blurred vision
Gastrointestinal disorders	Anorexia, flatulence, vomiting, stomatitis, gastritis, gastrointestinal disorder, sore throat
General disorders and administration site conditions	Asthenia, pain, back pain
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia
Nervous system disorders	Abnormal dreams, anxiety, dry mouth, hyperkinesia, paresthesia, increased sweating, euphoria, hallucinations
Renal and urinary disorders	Dysuria
Respiratory, thoracic and mediastinal disorders	Increased cough, rhinitis, dry nose
Skin and subcutaneous tissue disorders	Rash, urticaria

LONG-TERM PATIENT STUDY

Table 5 - Less Common Clinical Trial Adverse Drug Reactions (≤ 1%)

Body System	Adverse Reaction

Blood and lymphatic system disorders	Anemia, purpura
Cardiac disorders	Chest pain, chest pain substernal
Ear disorders	Tinnitus, deafness,
Eye disorders	Abnormal vision, blurred vision, lacrimation disorder
Gastrointestinal disorders	Eructation, stomatitis, vomiting, anorexia, duodenal ulcer, gastritis, gastrointestinal hemorrhage, increased appetite, melena, mouth ulceration, rectal bleeding, sore mouth, taste perversion
General disorders and administration site conditions	Asthenia, pain, back pain, face edema, hernia
Metabolism and nutrition disorder	Weight gain, alkaline phosphatase increase, BUN increased, excessive thirst, generalized edema, hyperuricemia
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, joint disorder
Nervous system disorders	Abnormal dreams, anxiety, depression, dry mouth, insomnia, nervousness, paresthesia
Renal and urinary disorders	Hematuria, increased urinary frequency, oliguria, polyuria
Respiratory, thoracic and mediastinal disorders	Dyspnea, asthma, epistaxis
Skin and subcutaneous tissue disorders	Pruritus, rash, burning sensation skin
Vascular disorders	Migraine

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

Clinical Trial Findings

Elevations of blood urea nitrogen (BUN) and creatinine have been reported in clinical trials with ketorolac.

8.5 Post-Market Adverse Reactions

Additional reports of adverse events temporally associated with ketorolac tromethamine 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 ketorolac tromethamine exposure.

The following post-marketing adverse experiences have been reported for patients who have received either formulation of ketorolac tromethamine:

Blood and lymphatic system disorders: postoperative wound hemorrhage, rarely requiring blood transfusion, thrombocytopenia, epistaxis, leukopenia, hematomata, increased bleeding time, agranulocytosis, aplastic anemia, hemolytic anemia, lymphadenopathy, pancytopenia, eosinophilia.

Cardiac disorders: pulmonary edema, bradycardia, arrhythmia, myocardial infarction, palpitations, cardiac failure, congestive heart failure.

Ear and labyrinth disorders: vertigo, hearing loss.

Eye disorders: visual disturbances, optic neuritis.

Gastrointestinal disorders: inflammation, bleeding (sometimes fatal, particularly in the elderly), obstruction of the upper or lower gastrointestinal tract, gastrointestinal hemorrhage, peptic ulceration, gastrointestinal perforation, acute pancreatitis, abdominal pain/discomfort, melena, esophagitis, hematemesis, ulcerative stomatitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), heartburn.

General disorders and administration site conditions: pallor, malaise, fatigue, pyrexia (chills and fever).

Hepatobiliary disorders: hepatitis (some cases of hepatitis have been fatal), jaundice, liver failure, cholestatic jaundice.

Immune system disorders: bronchospasm, laryngeal edema, tongue edema, asthma, hypotension, flushing, rash, anaphylaxis, angioedema and anaphylactoid reactions. Such reactions have occurred in patients with no prior history of hypersensitivity.

Infections and infestations: infection, conjunctivitis.

Investigations: raised serum urea and creatinine, abnormal liver function tests, prolonged bleeding time.

Metabolism and nutrition disorders: hyponatremia, hyperkalemia, hyperglycemia.

Musculoskeletal and Connective Tissue Disorders: muscle weakness.

Nervous system disorders: convulsions, hyperkinesia, hearing loss, aseptic meningitis, extrapyramidal symptoms, coma, taste abnormality, drowsiness, light-headedness.

Pregnancy, puerperium and perinatal conditions: oligohydramnios, neonatal renal impairment.

Psychiatric Disorders: abnormal dreams, hallucinations, psychotic reactions, abnormal thinking, impaired concentration ability, confusion.

Renal and urinary disorders: acute renal failure, flank pain with or without hematuria and/or azotemia, nephritis, hemolytic uremic syndrome, urinary retention, interstitial nephritis,

nephrotic syndrome, renal disease, renal papillary necrosis.

Reproductive system and breast disorders: female infertility.

Respiratory, thoracic and mediastinal disorders: respiratory depression, pneumonia, eosinophilic pneumonitis.

Skin and subcutaneous tissue disorders: Lyell's syndrome, bullous reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), exfoliative dermatitis, maculopapular rash, urticaria, photosensitive dermatitis, erythema multiforme, ecchymoses, skin eruptions, alopecia, erythema nodosum, photosensitivity reactions and angioneurotic oedema. A few case reports have been published of pseudoporphyria associated with diclofenac administration.

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued, and the patient monitored.

Vascular disorders: hypotension, hypertension, pallor, flushing, vasculitis.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) is associated with increased risk of arterial thrombotic events (for example myocardial infarction or stroke). See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- **NSAIDs:** MINT-KETOROLAC is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risk of inducing serious NSAID related side effects. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions.
- **Pentoxifylline**: The concomitant use of MINT-KETOROLAC and pentoxifylline is contraindicated due to an increased risk of bleeding. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions.
- **Probenecid**: The concomitant use of MINT-KETOROLAC and probenecid is contraindicated due to the significant increase in ketorolac plasma levels (approximately three-fold increase) and terminal half-life (approximately two-fold increase). See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions.

9.3 Drug-Behavioural Interactions

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

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

9.4 Drug-Drug Interactions

Protein Binding

Ketorolac tromethamine is highly bound to human plasma protein (mean 99.2%) and binding is independent of concentration. The *in vitro* binding of warfarin to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs. 99.3% binding with ketorolac tromethamine concentrations of 5 mcg/mL to 10 mcg/mL). Ketorolac tromethamine does not alter digoxin protein binding.

Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, paracetamol, phenytoin, tolbutamide and piroxicam did not alter ketorolac tromethamine protein binding. Because MINT-KETOROLAC is a highly potent medicine and present in low concentrations in plasma, it would not be expected to displace other protein bound medicines significantly.

Enzyme Induction / Inhibition

There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits the hepatic enzymes capable of metabolising itself or other medicines. Hence, MINT-KETOROLAC would not be expected to alter the pharmacokinetics of other medicines due to enzyme induction or inhibition mechanisms.

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 6 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) or other NSAIDs	CT	↑ Serious safety effects ↑ risk of bleeding	The use of MINT-KETOROLAC in addition to most NSAIDs, including over-the-counter ones (such as ibuprofen) for analgesic and/or anti-inflammatory effects is usually contraindicated because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. See 7 WARNINGS AND PRECAUTIONS. The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions. Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1. *In vitro* studies indicated that, at therapeutic concentrations of salicylates (300 mcg/mL), the binding of ketorolac tromethamine was reduced from approximately 99.2% to 97.5% representing a potential two-fold increase in unbound ketorolac tromethamine plasma levels. When ketorolac tromethamine is administered with aspirin, its protein binding is reduced, although the clearance of free ketorolac tromethamine is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant use of MINT-KETOROLAC and aspirin is contraindicated because of the potential of increased adverse effects and increased risk of bleeding. See 2 CONTRAINDICATIONS and 9.1 Serious Drug Interactions.
Antacids	CT		There is no definitive evidence that the concomitant administration of histamine H2-

Proper/Common name	Source of Evidence	Effect	Clinical comment
			receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of ketorolac tromethamine therapy when and if these adverse reactions appear.
Anti-coagulants	CT	↑ Bleeding	Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of bleeding. In a study involving 12 adult volunteers, ketorolac tromethamine tablets were co-administered with a single-dose of 25 mg warfarin, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine dosed IV or IM was given with two doses of 5000 U of heparin to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored. The effects of warfarin and NSAIDs, in general, on GI bleeding are synergistic, such that the users of both drugs together have a risk of serious GI bleeding higher than the users of either drug alone. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, low-molecular weight heparin and dextrans. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24 to 48

Proper/Common name	Source of Evidence	Effect	Clinical comment
			hours after ketorolac tromethamine is discontinued. Concurrent therapy of MINT-KETOROLAC with warfarin requires close monitoring of the international normalized ratio (INR). See 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-coagulants.
Antiepileptic Drugs	C	Increase in seizures	Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and antiepileptic drugs (phenytoin, carbamazepine). During concomitant use of MINT-KETOROLAC and antiepileptic drugs, monitor patients for seizures.
Anti-hypertensives	T	↓ Angiotensin converting enzyme (ACE) inhibitors Acute renal failure and hyperkalemia	NSAIDs may diminish the anti-hypertensive effects 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, Renal.
Anti-platelet Agents (including ASA)	CT	↑ Bleeding	There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as MINT-KETOROLAC. See 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-platelet Effects.
Cyclosporin	CT	Hyperkalemia ↑ Cyclosporin's nephrotoxicity	Concomitant use of MINT-KETOROLAC and cyclosporin may increase cyclosporin's nephrotoxicity. During concomitant use of MINT-KETOROLAC and cyclosporin, monitor patients for signs of worsening renal function. See 7 WARNINGS

Proper/Common name	Source of Evidence	Effect	Clinical comment
			AND PRECAUTIONS, Renal.
Digoxin	T	↑ Cardiac failure ↓ GFR ↑Digoxin	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides. Concomitant administration of an NSAID with digoxin can result in an increase in digoxin concentrations which may result in digitalis toxicity. Increased monitoring and dosage adjustments of digitalis glycosides may be necessary during and following concurrent NSAID therapy. Ketorolac tromethamine does not alter digoxin protein binding.
Diuretics	CT	↓Diuretics ↑ Nephrotoxicity	Clinical studies as well as post-marketing observations have shown that ketorolac tromethamine can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy. Ketorolac tromethamine reduces the diuretic response to furosemide by approximately 20% in normovolemic subjects, so particular care should be taken in patients with cardiac decompensation. See 7 WARNINGS AND PRECAUTIONS, Renal. Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.
Glucocorticoids	CT	↑GI ulceration and bleeding	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. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Lithium	CT	↑ Lithium	Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur. Some NSAIDs have been reported to inhibit renal lithium clearance, leading to an increase in plasma lithium concentrations and potential lithium toxicity. The effect of ketorolac tromethamine on lithium plasma levels has not been studied. Cases of increased lithium plasma concentrations during therapy with ketorolac tromethamine have been reported.
Methotrexate	C	↑ Methotrexate	Caution is advised in the concomitant administration of methotrexate and NSAIDs, as this has been reported to reduce the clearance of methotrexate, thus enhancing its toxicity. In case combination treatment with methotrexate and NSAIDs is necessary, blood cell count and the renal function should be monitored. Concomitant administration of NSAIDs with a potentially myelotoxic drug, such as methotrexate, appears to be a predisposing factor to the onset of a cytopenia.
Mifepristone	T	↓ Mifepristone	NSAIDs should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.
Nephrotoxic Agents	T	Nephrotoxic activity	The use of medicines with nephrotoxic activity (e.g. aminoglycoside antibiotics) should be avoided when using MINT-KETOROLAC.
Nondepolarizing Muscle Relaxants	CT	Apnea	In post-marketing experience there have been reports of a possible interaction between ketorolac tromethamine IV/IM and nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied. During concomitant use of MINT-KETOROLAC and nondepolarizing muscle relaxants, monitor patients for apnea.
Opioids	C		Ketorolac has been shown to reduce the need

Proper/Common name	Source of Evidence	Effect	Clinical comment
			for concomitant opioid analgesia when it is given for the relief of postoperative pain.
Pemetrexed	CT	↑ Increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity	Concomitant use of ketorolac tromethamine and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity. During concomitant use of ketorolac tromethamine and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Pentoxifylline	T	↑Bleeding	When ketorolac tromethamine is administered concurrently with pentoxifylline, there is an increased tendency to bleeding. The concomitant use of MINT-KETOROLAC and pentoxifylline is contraindicated.
Probenecid	T	↑ketorolac tromethamine	Concomitant administration of ketorolac tromethamine and probenecid results in the decreased clearance and volume of distribution of ketorolac and a significant increase in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 mcg/h/mL) and terminal half-life (increased approximately 2-fold from 6.6 to 15.1 hours). Therefore, concomitant use of MINT-KETOROLAC

Proper/Common name	Source of Evidence	Effect	Clinical comment
			and probenecid is contraindicated.
Psychoactive Drugs	C	Hallucinations	Hallucinations have been reported when ketorolac tromethamine was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam). During concomitant use of MINT-KETOROLAC and psychoactive drugs, monitor patients for hallucinations.
Quinolone antibiotics	CT	↑ Risk of convulsions	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Selective Serotonin Reuptake Inhibitors (SSRIs)	T	↑GI ulceration and bleeding	Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding. Caution should be used when NSAIDs are administered concomitantly with SSRIs. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal.
Tacrolimus	T	Risk of nephrotoxicity	There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine	CT	↑ Risk of hematological toxicity	NSAIDs given with zidovudine increase the risk of hematological toxicity. There is evidence of an increased risk of hemarthroses and hematoma in HIV (+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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

9.5 Drug-Food Interactions

Oral administration of ketorolac tromethamine tablets after a high-fat meal may result in decreased peak and delayed time-to-peak concentrations of ketorolac by about one hour.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

MINT-KETOROLAC (ketorolac tromethamine) is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity mediated by peripheral effects. The mechanism of action of ketorolac, like that of other NSAIDS, is not completely understood, but is believed to be related to prostaglandin synthetase inhibition.

Pain relief is comparable following the administration of ketorolac by intramuscular or oral routes. The peak analgesic effect occurs at 2 to 3 hours post-dosing with no evidence of a statistically significant difference over the recommended dosage range. The greatest difference between large and small doses of ketorolac tromethamine administered by either route is in the duration of analgesia.

10.3 Pharmacokinetics

The pharmacokinetics are linear following single and multiple dosing. Steady state plasma levels are attained after one day of Q.I.D. dosing.

Following oral administration, peak plasma concentrations of 0.7 to 1.1 mcg/mL occur at an average of 44 minutes after a single 10 mg dose. The terminal plasma elimination half-life ranges between 2.4 and 9.0 hours in healthy adults, and between 4.3 and 7.6 hours in elderly subjects (mean age 72 yrs). A high fat meal decreases the rate, but not the extent, of absorption of oral ketorolac tromethamine. The use of an antacid has not been demonstrated to affect the pharmacokinetics of ketorolac.

Following intramuscular administration, peak plasma concentrations of 2.2 to 3.0 mcg/mL occur an average of 50 minutes after a single 30 mg dose. The terminal plasma half-life ranges between 3.5 and 9.2 hours in young adults and between 4.7 and 8.6 hours in elderly subjects (mean age = 72 years).

In renally impaired patients there is a reduction in clearance and an increase in the terminal half-life of ketorolac tromethamine (see Table 7 below).

The parenteral administration of ketorolac tromethamine has not been demonstrated to affect the hemodynamics of anesthetized patients.

Absorption

Ketorolac tromethamine was rapidly (T_{max} ranged from 0.25 to 1.5 hours) and completely absorbed after oral and IM doses in humans (>99%).

Distribution:

The volume of distribution of ketorolac was estimated following intravenous dosing and in humans it averaged 0.15 L/kg.

Ketorolac was highly protein bound in human (99.2%). Binding was concentration independent.

Clearance and Half-life: The pharmacokinetics of ketorolac in man following single or multiple intramuscular doses are linear. Steady state plasma levels are achieved after dosing every 6 hours for one day. No changes in clearance occurred with chronic dosing. In humans, the plasma half-life averaged 6.0 hours. Total plasma clearance averaged 0.35 mL/min/kg in humans.

Metabolism:

Ketorolac is largely metabolized in the liver. The major metabolic path of ketorolac in humans is glucuronic acid conjugation. P-hydroxylation is an additional minor pathway.

In vitro and *in vivo* studies demonstrated that ketorolac does not induce or inhibit its own metabolism or the metabolism other drugs such as aniline, ethylmorphine and hexobarbital, upon multiple dosing.

A moderate first pass metabolism (about 20%) was observed in humans following oral doses.

The metabolism and excretion patterns of ketorolac and its metabolites were similar following p.o., i.v. and i.m. dosing in the species studied. Ketorolac accounted for most of the radioactivity circulating in the plasma and averaged 96% in humans. Conjugates of ketorolac were not detected in plasma in appreciable amounts. However, the p-hydroxy metabolite (which is essentially inactive when compared to ketorolac) was detected in the plasma. Ketorolac and its metabolites were excreted predominantly in the urine and averaged 92% in humans.

Elimination

The primary route of excretion of ketorolac tromethamine and its metabolites (conjugates and the p-hydroxy metabolite) is in the urine (91.4%) with the remainder (6.1%) being excreted in the feces.

Special Populations and Conditions

- **Pediatrics (<18 years of age)** ketorolac tromethamine is contraindicated in children and adolescents aged less than 18 years.
- **Geriatrics (≥65 years of age)** The terminal plasma half-life of ketorolac is prolonged compared to young healthy volunteers to an average of 7 hours (ranging from 4.3 to 8.6 hours). The total plasma clearance may be reduced compared to young healthy volunteers, on average to 0.019 L/h/kg.
- **Pregnancy and Breast-feeding** ketorolac tromethamine is contraindicated in third trimester of pregnancy and breast-feeding women.
- **Hepatic Insufficiency** Patients with impaired hepatic function do not have any clinically important changes in ketorolac pharmacokinetics, although there is a statistically significant prolongation of T_{max} and terminal phase half-life compared to young healthy volunteers.
- **Renal Insufficiency** Elimination of ketorolac is decreased in patients with renal

impairment as reflected by a prolonged plasma half-life and reduced total plasma clearance when compared to young healthy subjects. The rate of elimination is reduced roughly in proportion to the degree of renal impairment except for patients who are severely renally impaired, in whom there is higher plasma clearance of ketorolac than estimated from the degree of renal impairment alone.

Table 7 - The influence of age, liver and kidney function on the clearance and terminal half-life of ketorolac tromethamine[1]

Types of Subjects	Total Clearance (in L/h/kg)[2]	Terminal Half Life (in hours)
	MEAN (range)	MEAN (range)
Normal Subjects Oral (n=77**)**	0.025 (0.013-0.050)	5.3 (2.4-9.0)
Healthy Elderly Subjects Oral (n=12) (mean age = 72, range = 65-78)	0.024 (0.018-0.034)	6.1 (4.3-7.6)
Patients with Hepatic Dysfunction Oral (n=13)	0.033 (0.019-0.051)	4.5 (1.6-7.6)
Patients with Renal Impairment Oral (n=9) (serum creatinine 1.9-5.0 mg/dL)	0.016 (0.007-0.052)	10.8 (3.4-18.9)

[1] Estimated from 10 mg single oral doses of ketorolac tromethamine
[2] Litres/hour/kilogram

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C -30°C) with protection from light and moisture.

Keep out of reach from children.

12 SPECIAL HANDLING INSTRUCTIONS

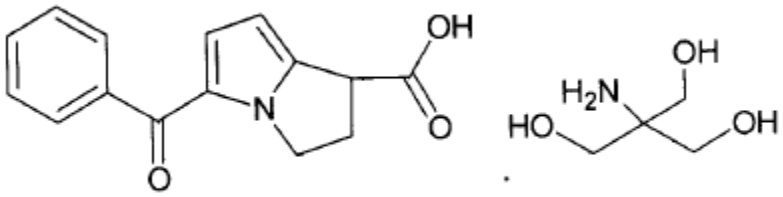
None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	ketorolac tromethamine
Chemical name:	(±)-5-Benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1, 3-propanediol
Molecular formula and molecular mass:	$C_{19}H_{24}N_2O_6$; 376.40 g/mol
Structural formula:	



Physicochemical properties:	ketorolac tromethamine (pKa = 3.46) is an off-white to white crystalline powder. It is freely soluble in water and methanol, slightly soluble in tetrahydrofuran, 190 proof and 200 proof ethanol and practically insoluble or insoluble in acetone, dichloromethane, toluene, ethylacetate, dioxane, hexane, butanol, and acetonitrile. The pH of a 1% (w/v) solution in distilled water is 5.7-6.7. Its melting point is about 162°C with decomposition.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

14.2 Comparative Bioavailability Studies

A double-blinded, randomized, two-treatment, two-sequence, two-period, two way crossover, single oral dose comparative bioavailability study of MINT-KETOROLAC 10 mg tablets (Mint Pharmaceuticals Inc.) and TORADOL® 10 mg tablets (Hoffmann-La Roche Limited) was conducted in healthy, adult, human male subjects under fasting conditions. Comparative bioavailability data from 26 subjects that were included in the statistical analysis are presented in the following table:

Table 8 – Summary Table of the Comparative Bioavailability Data

Ketorolac (1 x 10 mg) Geometric mean Arithmetic mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of geometric means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	4602.00 4678.04 (18.05)	4672.95 4745.83 (17.85)	98.5	(94.9, 102.2)
AUC_I (ng·h/mL)	4831.88 4907.73 (17.66)	4889.40 4968.49 (18.34)	98.8	(95.4, 102.4)
C_{MAX} (ng/mL)	1229.48 1255.48 (19.30)	1253.75 1292.73 (23.47)	98.1	(88.5, 108.6)
T_{MAX}[3] (h)	0.50 (0.33, 3.00)	0.50 (0.17, 2.00)		
$T_{½}$[4] (h)	4.98 (23.02)	4.90 (24.55)		

[1] MINT-KETOROLAC (ketorolac tromethamine) 10 mg Tablets, Mint Pharmaceuticals Inc.
[2] TORADOL® (ketorolac tromethamine) 10 mg Tablets of Hoffmann-La Roche Limited, purchased in Canada
[3] Expressed as the median (range) only.
[4] Expressed as the arithmetic mean (CV %) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity Studies

Animal	Strain	Sex	Route	LD_{50} (mg/kg)
Mouse	HLA-SW/ICR	F	Oral	approx. 400
Mouse	HLA-SW/ICR	M/F	Oral+	529 (281-1540)*
Rat	COX-SD	F	Oral	112 (68-191)*
Rat	COX-SD	M/F	Oral+	100-400
Mouse	HLA-SW/ICR	F	i.p.	>400
Mouse	HLA-SW/ICR	M/F	i.p.+	473 (315-771)*
Rat	COX-SD	F	i.p.	158 (101-248)*
Rat	COX-SD	M/F	i.p.+	100-400

Note: * 95% confidence interval

+ studies with ketorolac tromethamine; all others with ketorolac free acid. All doses were administered in solution form.

Administration of the free acid of ketorolac at a dose of 200 mg/kg, p.o. in 1 male and 1 female cynomolgus monkey caused both monkeys to vomit after dosing. Other changes seen in the female included diarrhea and anorexia starting 5 days after dosing. The male monkey gained weight while the female had weight loss. Both animals had decreased hemoglobin and hematocrit and survived the 2 week post dose period.

In another study, the identical dose of ketorolac tromethamine salt caused vomiting in the female. No other clinical signs were recorded for this animal. The male monkey appeared normal throughout the study duration.

Sensitization: The sensitization potential of a 0.1% solution of ketorolac tromethamine was evaluated in male guinea pigs. Ketorolac tromethamine did not cause sensitization when tested in the guinea pig model.

Vein Irritation: An intravenous formulation containing ketorolac tromethamine at a concentration of 10 mg/mL was injected into the marginal ear vein of the left ear of each of 6 rabbits (New Zealand albino). The right ear served as a sham control. No evidence of vein irritation was seen following gross or microscopic pathological examinations.

An intravenous formulation containing 10% ethanol and ketorolac tromethamine at a concentration of 10 or 30 mg/mL was injected into the marginal ear vein of the left ears of 6 rabbits (New Zealand albino). The right ear received vehicle only. There was no evidence of drug-related irritation in-life. Minimal irritation was noted microscopically in some animals that received the vehicle or drug formulations.

Sub chronic Toxicity Studies

Oral: Ketorolac was administered to groups of male and female mice at doses of 0 (vehicle

control), 0.25, 1.0, 4.0 or 16.0 mg/kg/day for a period of 4 weeks.

No drug related change was seen in the mice receiving 0.25 mg/kg/day. In mice receiving the higher doses, dose related changes included decreased activity, pallor, unthrifty appearance, wasting and rough coat. Treatment related deaths occurred in the high dose (16 mg/kg/day) group only (4/6 males and 5/6 females). Food intakes of the female mice in groups receiving 1.0 or 4.0 mg/kg/day were significantly lower than control values. In treated male groups, food intakes were comparable to control values throughout the study.

Hematologic parameters measured revealed decreased hemoglobin and hematocrit levels for groups receiving 4.0 or 16.0 mg/kg/day and elevated total leukocyte and neutrophil counts in the high dose group animals. No biologically meaningful changes were found in any of the plasma chemistry parameters or urinalysis. Gastrointestinal inflammation, erosions and/or ulcers were present in the high dose animals only. No drug related pathological change was present in mice from other dose groups.

Daily oral administration of ketorolac to monkeys at doses of 0.0 (vehicle control), 0.5, 2, 8 or 32 mg/kg/day for 4 weeks resulted in clinical signs of toxicity and hematologic and pathologic effects at all dose levels. Clinically, a few isolated instances of dark colored urine, vomiting and dark colored feces (fecal blood) were seen in all dose groups but not in controls. There was a slight decrease in hemoglobin and hematocrit levels mainly in the high dose group animals. Other parameters, such as body weight, ophthalmoscopy, clinical chemistry and urinalysis were all comparable to control values. Gastric erosions were observed in some animals at all dose levels, while gastric ulceration and hemorrhage were seen in some animals receiving 8 or 32 mg/kg/day. Chronic colitis was seen in 3 out of 4 monkeys treated with the highest dose.

Intravenous: Intravenous administration of ketorolac tromethamine to rabbits and monkeys at doses of 0 (vehicle), 0.5, 1.25 or 2.5 mg/kg/day for 2 weeks was well tolerated with no clinically significant treatment related effects.

Intramuscular: Rabbits were administered ketorolac tromethamine intramuscularly at daily doses of 0 (saline control), 10 or 15 mg for 29 consecutive days. Each group comprising 3 males and 3 females received a dose volume of 0.5 mL/animal.

There were no treatment related clinical changes during the study. Minimal to slight hematologic changes occurred in some treated animals. Gross and/or microscopic examinations of the injection sites revealed focal hemorrhage, muscle fiber degeneration and mixed leukocyte infiltration in all groups.

Five groups, each comprised of 3 male and 3 female cynomolgus monkeys, were administered intramuscular injections of saline, vehicle or 4.5, 9.0 or 13.5 mg/kg/day of ketorolac tromethamine for 3 months. Injections were given thrice daily with dose volumes of 0.15, 0.15, 0.05, 0.10 or 0.15 mL/kg/dose for saline, vehicle, low, mid and high dose groups, respectively. The sites injected on the first day and last 7 days of injections were noted for histological examination.

There were no clinical signs of drug related systemic toxicity. However, the incidence and severity of lacerations and ulcers of the extremities (limbs and tail) were increased in the drug

treated groups compared to the controls. These lesions were probably the result of bite wounds and the analgesic effect of the drug may have reduced the normal avoidance behavior in response to painful stimuli.

No drug related changes in body weight gain, eye morphology or clinical pathologic results were observed except for slight increases in blood urea nitrogen (BUN) in high and mid dose females.

Local irritation at the injection site was noted in animals from all treatment groups. In conclusion, doses of 4.5, 9.0, and 13.5 mg/kg of ketorolac tromethamine given to monkeys by three times daily intramuscular injections for 3 months caused essentially no drug related systemic toxicity.

Chronic Toxicity Studies

Mice (30 males and 30 females per group) were given either a placebo diet or drug-diet mixtures equivalent to an estimated daily dose of 0 (placebo), 3.3, 10 or 30 mg ketorolac tromethamine/kg/day for 6 months.

Treatment related clinical changes were seen in animals in the mid and high dose groups and these included pallor, rough coat, unthrifty appearance, wasting, abdominal enlargement, decreased activity, labored respiration and decreased body temperature. In general, trends of slightly lower body weight and lesser feed intake were observed in treated males and females relative to controls. No drug related ocular lesions were observed in animals.

Prior to termination of the study, 3 of 6 low dose, 9 of 60 mid dose and 52 of 60 high dose animals either died or had to be sacrificed because of poor clinical condition. The cause of debilitation or death of most of the mid and high dose animals was related to erosions and ulcerations in the stomach and large and/or small intestines. Many of these animals were anemic. At all dose levels, renal inflammatory lesions, especially in females were found. An apparent interruption of ovarian cyclic activity was noted histologically. Prostaglandin synthetase inhibitors have been reported to block ovulation by central activity.

Cynomolgus monkeys (4 males and 4 females/group) were administered ketorolac tromethamine orally, twice daily for a period of 6 months at doses of 0 (vehicle control), 0.75, 2.95 or 11.75 mg/kg/day.

There were no treatment related clinical changes or changes in laboratory tests with the exception of slightly elevated urea nitrogen levels in the ketorolac treated animals. The principal gross pathologic finding was pallor of the renal papilla and cortex in both males and females that received the test compound. The gross changes correlated microscopically with minimal to mild increases in interstitial matrix in the renal papilla of the mid and high dose animals only. No specific microscopic change was present in renal cortex which correlated with cortical pallor.

Two groups each with 5 male and 5 female cynomolgus monkeys were administered once daily 0.75 or 2.62 mg/kg of ketorolac tromethamine for 12 months. Two additional groups each with 8 males and 8 females received vehicle only or 9 mg/kg of ketorolac tromethamine for 12 months. All groups received 1.5 mL/kg/day of formulation administered into the stomach by

nasal catheter. Three males and three female monkeys from the high dose and vehicle treated groups had a recovery period from dosing of months and then were given clinical laboratory analysis and a complete necropsy at the end of the 12 month dosing period.

Two females (one control and one mid-dose diagnosed with gastroenteropathy and enteropathy respectively) were sacrificed in a moribund condition at week 11 while one female diagnosed with pneumonia was sacrificed at study week 31. Causes of death were varied and not considered related to the test compound.

There were no drug related differences in the clinical condition of the surviving animals. The males showed a dose related decrease in RBC count, hemoglobin, hematocrit, mean corpuscular hemoglobin and hemoglobin concentration. The females were not affected to the same extent as the males but did show marginal decreases in some parameters at some time intervals (mainly in the highest dose group). Normalization of these tests occurred in animals after a 2 month drug free recovery period. The males had a significant increase in BUN, the magnitude of which increased with the dose and time of exposure to the drug. The females had no change in BUN, but the high dose group had a significant increase in serum creatinine at the 9 and 12 month intervals.

Oral administration of 9 mg/kg of ketorolac tromethamine for 12 months caused minimal renal microscopic pathologic changes which included increased intertubular matrix in the papilla and intratubular mineralization in the cortical, medullary and papillary tubules. Those animals given a 2 month period of recovery from dosing showed absences of morphologic damage.

These findings suggest that only mild, reversible kidney changes occurred with high doses of ketorolac tromethamine after one year of treatment. This conclusion is supported by the minimal histopathologic effects observed and by the absence of effects after the recovery period.

Genotoxicity:

In vitro mutagenic studies were performed with ketorolac, ketorolac tromethamine and tromethamine using 5 strains of bacteria and one of yeast.

Tests were carried out with and without mammalian microsomal activation. None of the compounds tested were mutagenic in any of these test systems. Ketorolac tromethamine was also negative in the *in vivo* mouse micronucleus test.

Carcinogenicity:

The carcinogenic potential of ketorolac tromethamine was assessed in an 18 month feeding study. Fifty Swiss-Webster albino mice were randomly assigned to receive 0.5, 1.0 or 2.0 mg/kg/day of ketorolac tromethamine in their diet. A control group of 100 animals of each sex received the same diet without ketorolac. The duration of the study was 78 weeks. However, males in the highest dose group received control diet for the last 3 weeks of the study due to the high mortality rate in that group relative to controls. Female survival was not affected. All animals received a complete necropsy.

The average body weight of the high dose males was generally lower than that of the controls

during the second half of the study. No such effect was evident in males in the lower dose groups or in females. Since the average food intake was similar for all dose groups throughout the study, the difference in body weight was not the result of reduced food intake.

Histopathologic examinations revealed no treatment related increase in the incidence of any type of tumor. Enteritis, gastroenteropathy and peritonitis were seen primarily in the high dose group and were considered expected sequelae to high doses of an NSAID.

In conclusion, there was no evidence for a carcinogenic effect of ketorolac tromethamine in the mouse.

A 24 month feeding study was conducted in rats to assess the carcinogenic potential of ketorolac tromethamine. Fifty Sprague-Dawley rats of either sex were administered in their diet either 0.8, 2.0 or 5.0 mg ketorolac/kg body weight. A control group of 100 animals received the same diet without the drug.

No treatment related changes were noted in clinical condition except for a reddish discoloration of the urine which occurred more frequently in treated males than in controls. The survival times were significantly lower than controls in high dose males and mid and high dose females.

The body weights of the high dose group females were approximately 10% lower than the controls during the last 6 months of the study although no differences in food intakes were noted among the various groups. The high dose males had decreased erythroid parameters, elevated platelet count and a higher incidence of blood in the urine specimens. High dose males and females had elevated BUN and increased neutrophil and decreased lymphocyte counts. Mid and high dose females had a lower urinary specific gravity compared to control females.

There was no evidence for a carcinogenic effect of ketorolac tromethamine in rats.

Reproductive and Developmental Toxicology:

Fertility and Reproduction

Female Rat: A two generation study was conducted to evaluate the effects of ketorolac tromethamine on fertility and reproduction in female rats. Groups, each composed of 40 female rats, were administered drug-diet mixtures to achieve doses of 0 (placebo control), 1, 4 or 16 mg/kg/day. The P1 female rats were treated from 14 days before mating until gestation day 13 or until the F1 pups were weaned at 21 days postpartum. The reproductive performance of F2 pups was also evaluated.

No treatment-related effects were seen on the reproductive status at gestation day 13. Some treated females died during the study and the deaths were attributed to gastroenteropathy, nephropathy, or dystocia.

The length of gestation was significantly increased in the high-dose (P1 females) group (median 25 days) when compared to the controls (median 22 days). A slight increase in the length of gestation (median 22.5 days) was noted in the mid-dose group when compared to the controls. Decreased live litter sizes and survival indices were noted in the high-dose group when compared to controls. No pups from the high-dose group survived to day 4 of postnatal life.

Decreased survival indices (up to day 7) were noted in the mid-dose group when compared to controls. The maternal care and lactation data were comparable among the control, low and mid-dose groups. The clinical condition and body weights of surviving F1 pups were comparable among all groups. The postnatal behavioral and developmental evaluation of F1 pups indicated no treatment-related effects. The reproductive performance of the F1 pups and the neonatal survival of their offspring (F2 pups) were comparable among the groups.

In conclusion, dietary administration of ketorolac tromethamine to female rats prior to and during mating, gestation, parturition and lactation resulted in increased mortality among F0 dams and reduced F1 litter size at 16 mg/kg/day and prolonged gestation period and reduced neonatal survival at 4 and 16 mg/kg/day.

Male Rat: Four groups each with 25 male rats were dosed once daily by gavage with 0, 3.0, 6.0 or 9.0 mg/kg of ketorolac tromethamine. Males were dosed for 104 days prior to cohabitation with undosed females and continued to be dosed through the 14 day mating period. Mating units consisted of one dosed male and two untreated females. Approximately half of the females with evidence of mating were sacrificed at midgestation while the other half were allowed to litter and raise their pups until 21 days postpartum.

No drug-related changes in the clinical condition of the males were observed. Body weight and food intake were not affected by drug treatment. There were no drug-related differences in the number of males leaving evidence of mating, the pre-coital interval, or in the number impregnating females.

The females mated with high-dose males and sacrificed at midgestation had a significant preimplantation loss resulting in smaller litter sizes. However, there was no increase in the number of resorptions (post implantation loss) and no decreases in litter size of dams littering at term. Therefore, the reduced number of implantations in the high dose females was not considered to be a drug effect.

There were no differences between drug groups and the control group in regard to body weight, length of gestation, gestation index, lactation index, number of pups born alive and survival indices. Thus, administration of ketorolac tromethamine by gavage to male rats prior to and during the mating period resulted in no effects on male reproductive performance and no drug related effects in their offspring.

Teratology

Studies were conducted in rats and rabbits. Female rats (25 per group) were administered ketorolac tromethamine at doses of 0 (vehicle control), 0.1, 0.6 or 3.6 mg/kg/day by gavage, once daily from day 6 through day 15 of gestation.

At these doses no maternal toxicity or fetal anatomical abnormalities related to the administration of ketorolac tromethamine were observed.

In a second study, female rats which were administered ketorolac tromethamine 10 mg/kg orally by gavage once daily showed pallor, rough coat and lower body weight gains than the

control dams. One dam died on gestation day 15; duodenal ulceration and peritonitis considered to be treatment related were seen. No embryotoxicity or embryolethality were observed. External and skeletal or visceral examinations of fetuses did not reveal any teratogenic changes attributable to the test compound.

Administration of ketorolac tromethamine, to female rabbits during organogenesis (day 6 through day 18 of gestation) by gavage once daily at doses of 0.1, 0.6 or 3.6 mg/kg/day was not teratogenic.

There were no treatment related clinical changes during the course of the study. One mid dose animal died on gestation day 18 of undetermined cause. All other animals survived to the end of the study. A slight body weight loss was noted in the high dose animals and there was a slight dose related reduction in food consumption during days 6 through 11 of gestation.

There were no statistically significant or biologically meaningful differences in the number of litters with malformations in any of the treated groups when compared to the control group. Developmental and genetic variations in fetuses were comparable for all groups.

Juvenile Toxicity:

Perinatal and Postnatal Reproduction Study: Four groups, each of 25 female rats with evidence of mating were administered 0, 1.8, 4.8, or 9.0 mg/kg/day of ketorolac tromethamine once daily by gavage from day 15 of pregnancy until 21 days postpartum or until all of their pups died. Females that did not litter were treated until approximately 25 days following the last day of mating and then sacrificed for pregnancy determination. Pups found dead within the first four days after parturition received an external examination and a skeletal examination if possible.

Ketorolac tromethamine at a dose of 9.0 mg/kg/day increased the length of gestation, the number of dams found dead or killed for cause as a result of dystocia, the number of pups found dead at first observation and, the number of pups dying within the first seven days postpartum. The weight of male and female pups was also decreased at days 4 and 7 postpartum compared to the control group.

Ketorolac tromethamine at a dose of 4.8 mg/kg/day did not alter the length of gestation of dams littering normally but did increase the incidence of dams found dead or sacrificed for cause as a result of dystocia. The maternal effects observed at the two highest dose levels were expected for a drug of this class.

Ketorolac tromethamine at a dose of 1.8 mg/kg/day caused no alterations in the length of gestation, nature of parturition, pup survival or any other aspect of reproductive performance.

17 SUPPORTING PRODUCT MONOGRAPHS

1. TORADOL (Ketorolac Tromethamine Tablets, 10 mg), submission control 283292, Product Monograph, AA Pharma Inc. AUG 09, 2024

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]MINT-KETOROLAC

Ketorolac Tromethamine Tablets

Read this carefully before you start taking **MINT-KETOROLAC** 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 **MINT-KETOROLAC**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- MINT-KETOROLAC 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 MINT-KETOROLAC 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:

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

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

Pregnancy:

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

What is MINT-KETOROLAC used for?

MINT-KETOROLAC is used in adults for the short-term relief of moderate to moderately severe pain. It is usually used:

- after surgery (including dental procedures) or giving birth. The maximum duration of treatment is 5 days.
- for an injury causing muscle or joint pain. The maximum duration of treatment is 7 days.

How does MINT-KETOROLAC work?

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

What are the ingredients in MINT-KETOROLAC?
Medicinal ingredient: ketorolac tromethamine.

Non-medicinal ingredients: hypromellose, lactose monohydrate, macrogol 4000, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

MINT-KETOROLAC comes in the following dosage forms:
Tablets: 10 mg of ketorolac tromethamine.

Do not use MINT-KETOROLAC if:

- you have heart bypass surgery (planning to have or recently had).
- 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 ketorolac tromethamine or any other ingredients in MINT-KETOROLAC or 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 are in labour or giving birth.
- you have high potassium in the blood.

- you are going to have any major surgery.
- you are taking:
  - other NSAIDs, used to treat pain, fever and inflammation.
  - probenecid, used to treat gout.
  - pentoxifylline (also known as oxpentifylline), used to improve blood circulation.
- you are under 18 years of age.

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

- have a condition that makes you frail or weak.
- have high cholesterol.
- 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 recently had, or are going to have, surgery of the stomach or intestinal tract. MINT-KETOROLAC may worsen wound healing in your gut after surgery
- have other bleeding or blood problems.
- have immune system problems.
- have asthma.
- are pregnant, planning on becoming or become pregnant while taking MINT-KETOROLAC.
- are taking any other medicines.

Other warnings you should know about:

MINT-KETOROLAC may cause serious side effects, including:

- **Blood and bleeding problems**:
  - MINT-KETOROLAC can cause blood problems, bleeding and prolonged bleeding.
  - Taking MINT-KETOROLAC 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).

- **Aseptic meningitis** (inflammation of the protective lining of the brain that is not caused by an infection): Patients with autoimmune disorders are at a higher risk.

- **Serious skin reactions:** In rare cases, serious, life-threatening allergic and skin reactions have been reported with some NSAIDs, such as MINT-KETOROLAC. 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. MINT-KETOROLAC 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.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Infection: MINT-KETOROLAC may mask signs of an infection such as fever or muscle aches. If you notice other symptoms of infection (e.g., painful or frequent urination, sore throat, cough), tell your healthcare professional.

Surgery: Tell all your doctors, dentists, pharmacists and/or healthcare professionals that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Fertility in women: MINT-KETOROLAC 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 MINT-KETOROLAC. Talk to your healthcare professional if you have any questions about this.

Patients 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 MINT-KETOROLAC. They will monitor your health during and after treatment.

Driving and using machinery: MINT-KETOROLAC 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 MINT-KETOROLAC, do NOT drive or operate machinery.

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

- Check your blood pressure.
- Check your eyes. MINT-KETOROLAC 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.

Serious Drug Interactions

Do not take MINT-KETOROLAC with:

- acetylsalicylic acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation (e.g., celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen);
- pentoxifylline (also known as oxpentifylline), used to improve blood circulation;
- probenecid, used to treat gout.

Taking MINT-KETOROLAC with these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure you are taking these medicines.

The following may also interact with MINT-KETOROLAC:

- antacids, used to treat symptoms of excess stomach acid.
- medicines used to treat depression (antidepressants), like citalopram, fluoxetine, paroxetine, sertraline, and lithium.
- medicines used to treat high blood pressure, like enalapril, lisinopril, perindopril, ramipril, candesartan, irbesartan, losartan, and valsartan.
- medicines used to lower extra fluid levels (diuretics), like furosemide, and hydrochlorothiazide.
- medicines used as blood thinners or to prevent blood clots, like warfarin, clopidogrel, heparin, and dextrans.
- medicines used to treat seizures or epilepsy (antiepileptics), like carbamazepine and phenytoin.
- cyclosporin and tacrolimus, used to lower the risk of organ transplant rejection.
- methotrexate and pemetrexed, used to treat different cancers.
- digoxin, used to treat heart disorders.
- corticosteroids, used to treat inflammation, like glucocorticoids such as prednisone.
- mifepristone, used for abortions. MINT-KETOROLAC should not be taken for 8 to 12 days after taking mifepristone.
- medicines used to treat bacterial infections (antibiotics), like aminoglycosides and quinolone antibiotics.
- opioids, used to relive pain.
- thiothixene, used to treat schizophrenia.
- alprazolam, used to manage symptoms of anxiety.
- zidovudine, used to prevent and treat human immunodeficiency virus HIV.
- medicines used to treat muscle spasms and back pain (muscle relaxants).
- alcohol.

How to take MINT-KETOROLAC:

- Take exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- Your healthcare professional will check if MINT-KETOROLAC is working for you and if it is causing you any unwanted effects. They may change your dose depending on how you respond to MINT-KETOROLAC.
- To lessen stomach upset, take this medicine immediately after a meal (with food or milk). However, taking MINT-KETOROLAC with food may delay the onset of pain relief. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your healthcare professional.
- You should remain standing or sitting upright for about 15 to 30 minutes after taking this medicine. This helps to prevent irritation that may lead to trouble swallowing.
- **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.**

Usual dose:

<u>For pain relief after surgery (including dental procedures) or giving birth:</u>

- The usual dose is 10 mg every 4 to 6 hours as needed.
- Maximum duration of treatment: **5 days**.

<u>For pain relief for an injury causing muscle or joint pain:</u>

- The usual dose is 10 mg every 4 to 6 hours as needed.
- Maximum duration of treatment: **7 days**.

Overdose:

Signs of an overdose with MINT-KETOROLAC may include:

- nausea or vomiting;
- abnormally fast, slow or deep breathing;
- abdominal pain, ulcer or bleeding from the stomach or gut;
- kidney problems;
- high blood pressure;
- coma.

If you think you, or a person you are caring for, have taken too much MINT-KETOROLAC contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. 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 MINT-KETOROLAC?

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

Side effects may include:

- Nausea, vomiting, diarrhea, constipation, stomach upset, heartburn, indigestion, feeling gassy;
- Headache, dizziness, light-headedness;
- Feeling tired, trouble sleeping, abnormal dreams;
- Feeling of burning or prickling of the skin;
- Anxiety, nervousness;
- Thirst, dry mouth, sore throat, changes in tastes;
- Bruises, rash;
- Muscle pain/twitching/weakness;
- Mouth sores;
- Increased sweating;
- Bruising;
- Hair loss;
- Increased sensitivity to light.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever		✓	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	✓		
UNCOMMON			

Anaphylaxis/hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock			✓
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): Headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness		✓	
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		✓	
Congestive heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating		✓	
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 and renal papillary necrosis): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma, painful urination, chills, back pain)		✓	
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 (including asthma): increased shortness of breath, wheezing, difficulty breathing, cough, chest tightness, irregular heartbeat, lung infection, chest pain, fever			✓
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 ears, loss of hearing		✓	
Vertigo (a sense of severe spinning dizziness, light-headedness)		✓	
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, red or dry itchy skin, purple or red spots on skin			✓
UNKNOWN FREQUENCY			
Eye problems: blurred vision, loss of part or all of central vision, reduced colour vision, dimness of vision.		✓	

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store MINT-KETOROLAC at room temperature (15 to 30°C). Protect from light and moisture.
- Do NOT keep expired medicine or medicine no longer needed. Return to your healthcare professional**.**
- Keep out of sight and reach of children.

If you want more information about MINT-KETOROLAC:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.mintpharma.com, or by calling 1.877.398.9696.

This leaflet was prepared by Mint Pharmaceuticals Inc.

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