

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrAPO-KETOROLAC Injectable**

Ketorolac Tromethamine Injection

Solution, 30 mg/mL, Intramuscular

USP

Non-Steroidal Anti-Inflammatory Drug (NSAID)

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Date of Initial Authorization:  
June 4, 2001

Date of Revision:  
March 7, 2023

Submission Control Number: 268345

## RECENT MAJOR LABEL CHANGES

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

Intramuscular injection of APO-KETOROLAC Injectable (ketorolac tromethamine injection) is indicated for:

- the short-term management (not to exceed 2 days) of moderate to severe acute pain, including pain following major abdominal, orthopaedic and gynaecological operative procedures.

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

**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](#)).**

**Use of APO-KETOROLAC Injectable should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see [2 CONTRAINDICATIONS](#) and [7 WARNINGS AND PRECAUTIONS](#)).**

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

APO-KETOROLAC Injectable, 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):**

APO-KETOROLAC Injectable 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**

APO-KETOROLAC Injectable (Ketorolac Tromethamine) is contraindicated in:

- 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

- 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 haemorrhage.
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- severe uncontrolled heart failure
- known hypersensitivity to APO-KETOROLAC Injectable or to other NSAIDs, including any of the components/excipients see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#)
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see [7 WARNINGS AND PRECAUTIONS: Immune, Anaphylactoid Reactions](#))
- active gastric / duodenal / peptic ulcer, active GI bleeding
- inflammatory bowel disease
- cerebrovascular bleeding or other bleeding disorders
- coagulation disorders, post-operative patients with high haemorrhagic risk or incomplete haemostasis in patients with suspected or confirmed cerebrovascular bleeding.
- immediately before any major surgery and intraoperatively when haemostasis is critical because of the increased risk of bleeding
- severe liver impairment or active liver disease.
- moderate to severe renal impairment (serum creatinine >442 µmol/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, Fluid and Electrolyte Balance](#)).
- 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](#))
- neuraxial (epidural or intrathecal) administration of APO-KETOROLAC Injectable due to its alcohol content.
- concomitant use with probenecid (see [9.1 Serious Drug Interactions](#))
- concomitant use with pentoxifylline (also known as oxpentifylline) (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](#)).**

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

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

Use of NSAIDs, such as APO-KETOROLAC Injectable, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. (see also [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 APO-KETOROLAC Injectable.

- **Risk of Gastrointestinal (GI) Adverse Events (see [7 WARNINGS AND PRECAUTIONS: Gastrointestinal](#)).**
- Use of NSAIDs, such as APO-KETOROLAC Injectable, 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 APO-KETOROLAC Injectable during the first and second trimesters of pregnancy. Use of APO-KETOROLAC Injectable at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see [7.1.1 Pregnant Women](#)). APO-KETOROLAC Injectable is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see [2 CONTRAINDICATIONS](#)).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

Use of APO-KETOROLAC Injectable should be limited to the lowest effective dose for the shortest possible duration of treatment (see [1 INDICATIONS](#)).

#### Conversion from Parenteral to Oral Therapy

When ketorolac tromethamine 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. APO-KETOROLAC Injectable 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.

APO-KETOROLAC Injectable: The recommended usual initial dose is 10 to 30 mg, according to pain severity. Subsequent dosing may be 10 mg to 30 mg every 4 to 6 hours as needed to control pain. The lowest effective dose should be administered.

The administration of APO-KETOROLAC Injectable should be limited to short-term therapy (not to exceed 2 days) and the total daily dose should not exceed 120 mg. The risk of toxicity increases with longer use and at higher than recommended doses (see [7 WARNINGS AND PRECAUTIONS](#)). The administration of continuous multiple daily doses of ketorolac tromethamine has not been extensively studied. There has been limited experience with intramuscular dosing beyond 2 days since the vast majority of patients have transferred to oral medication or no longer required analgesic therapy after this time.

#### Renal Impairment

APO-KETOROLAC Injectable is contraindicated in patients with moderate to severe renal impairment (serum creatinine >442 mcml/L). APO-KETOROLAC Injectable should be used with caution in patients with lesser renal impairment (serum creatinine 170 to 442 mcml/L). Such patients should receive a reduced dose of APO-KETOROLAC Injectable, and their renal status should be closely monitored. It is recommended that the daily dose be reduced by half; a total daily dose of 60 mg should not be exceeded. Dialysis does not significantly clear ketorolac from bloodstream. See [2 CONTRAINDICATIONS](#), [7 WARNINGS AND PRECAUTIONS: Renal](#) and [10 CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Insufficiency](#).

### **Hepatic Impairment**

APO-KETOROLAC Injectable is contraindicated in patients with severe liver impairment or active liver disease. Caution should be observed in giving APO-KETOROLAC Injectable to patient with mild to moderate hepatic insufficiency. See [2 CONTRAINDICATIONS](#), [7 WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic](#) and [10 CLINICAL PHARMACOLOGY: Special Populations and Conditions, Hepatic Insufficiency](#).

### **Elderly, Frail or Debilitated Patients**

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

The lower end of the dosage range is recommended. The initial dose should be 10 mg. The total daily dose of APO-KETOROLAC Injectable in the elderly should not exceed 60 mg. See [7.1.4 Geriatrics](#).

### **4.4 Administration**

Parenteral drug products should be inspected visually for particulate material and discoloration prior to use.

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

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	30 mg/mL solution	alcohol, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

APO-KETOROLAC Injectable is available for intramuscular administration as 30 mg in 1 mL (3%) of ketorolac tromethamine in sterile solution. Each mL contains the non-medicinal ingredients: water for injection, 4.35 mg sodium chloride and 100 mg alcohol. The pH is adjusted between 6.9 - 7.9 with sodium hydroxide or hydrochloric acid. The sterile solution is clear, colourless to slightly yellow in colour.

APO-KETOROLAC Injectable 30 mg/mL is available in 1 mL single use vials. Boxes of 5, 10 and 20.

## 7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#)

### General

The long-term use of 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.

APO-KETOROLAC Injectable 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: Carcinogenicity, Mutagenicity](#)).

## Cardiovascular

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

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

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

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

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

## Endocrine and Metabolism

**Corticosteroids:** APO-KETOROLAC Injectable (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**

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 APO-KETOROLAC Injectable. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with APO-KETOROLAC Injectable, 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 Special Populations, Geriatrics](#)).

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

Caution should be taken if prescribing APO-KETOROLAC Injectable 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 H<sub>2</sub>-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.

### **Genitourinary**

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), haematuria 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 APO-KETOROLAC Injectable **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 haemophilia or platelet disorders should be carefully observed when APO-KETOROLAC Injectable is administered.

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

Even with therapeutic INR monitoring, increased bleeding may occur.

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

In patients receiving anticoagulants, the risk of intramuscular haematoma formation from ketorolac tromethamine is increased.

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

Ketorolac tromethamine given with 2 doses of 5000 U of heparin to 11 healthy volunteers, resulted in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 minutes) compared to a mean of 6.0 min (3.4 to 7.5 minutes) for heparin alone and 5.1 minutes (3.5 to 8.5 minutes) for placebo.

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 and other NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time. Ketorolac tromethamine does not affect

platelet count, prothrombin time (PT) or partial thromboplastin time (PTT).

Unlike acetylsalicylic acid (ASA), NSAIDs' 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 ketorolac tromethamine 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 APO-KETOROLAC Injectable should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

**Haemorrhage and perioperative use of APO-KETOROLAC Injectable:** Post-operative haematomas and other symptoms of wound bleeding have been reported in association with the perioperative use of intramuscular ketorolac tromethamine. Physicians should be aware of the potential risk of bleeding when haemostasis is critical in cases such as, but not limited to, resection of the prostate, tonsillectomy or cosmetic surgery. APO-KETOROLAC Injectable is contraindicated in patients who have coagulation disorders. If APO-KETOROLAC Injectable is to be administered to patients who are receiving drug therapy that interferes with haemostasis, careful observation is advised. See [2 CONTRAINDICATIONS](#)

### **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.

APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable 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](#), [10.3 Pharmacokinetics](#)).

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

### **Immune**

**Anaphylactoid Reactions:** As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to ketorolac tromethamine. Counteractive measures must be available when administering the first dose of APO-KETOROLAC Injectable. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving ketorolac tromethamine. APO-KETOROLAC Injectable should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see [2 CONTRAINDICATIONS](#)).

**ASA-Intolerance:** APO-KETOROLAC Injectable 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.

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

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

## Monitoring and Laboratory Tests

The following testing or monitoring is recommended for various populations of patients taking APO-KETOROLAC Injectable. 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](#) 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 DRUG INTERACTIONS](#)

**Hepatic:** Serum transaminase and bilirubin should be monitored during APO-KETOROLAC Injectable therapy. See [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#).

**Ophthalmologic:** An ophthalmologic examination may be required. See [7 WARNINGS AND PRECAUTIONS, Ophthalmologic](#).

**Pregnancy:** If APO-KETOROLAC Injectable is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on APO-KETOROLAC Injectable be closely monitored for amniotic fluid volume since APO-KETOROLAC Injectable may result in reduction of amniotic fluid volume and even oligohydramnios). APO-KETOROLAC Injectable is contraindicated for use in the third trimester of pregnancy. See [2 CONTRAINDICATIONS](#), [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#), [7.1.1 Pregnant Women](#).

**Renal:** Serum creatinine, creatinine clearance and serum urea should be checked in patient during APO-KETOROLAC Injectable therapy. 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 APO-KETOROLAC Injectable. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

### Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such

symptoms develop, APO-KETOROLAC Injectable 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: coronary artery bypass graft surgery](#), see [7 WARNINGS AND PRECAUTIONS: Haemorrhage and perioperative use of APO-KETOROLAC Injectable](#))

### **Psychiatric**

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

### **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, haematuria, 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 APO-KETOROLAC Injectable, 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 tromethamine. APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable, 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 APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see [2 CONTRAINDICATIONS](#)).

### **Reproductive Health: Female and Male Potential**

**Fertility:** The use of APO-KETOROLAC Injectable, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of APO-KETOROLAC Injectable 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 ketorolac tromethamine, 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

**Pregnant Women: APO-KETOROLAC Injectable is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY).**

Caution is recommended in prescribing APO-KETOROLAC Injectable during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

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

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if APO-KETOROLAC Injectable 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.

APO-KETOROLAC Injectable 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

APO-KETOROLAC Injectable is contraindicated in breast-feeding women (see [2 CONTRAINDICATIONS](#)).

### 7.1.3 Pediatrics

**Pediatrics (< 18 years of age):** APO-KETOROLAC Injectable is contraindicated in pediatric patients. See [2 CONTRAINDICATIONS](#).

### 7.1.4 Geriatrics

**Geriatrics:** Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

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. This is particularly true in elderly patients who receive an average daily dose greater than 60 mg/day of ketorolac tromethamine. Because ketorolac is cleared somewhat more slowly by the elderly (see [10.3 Pharmacokinetics](#)), extra caution and the lowest effective dose should be used (see [4.2 Recommended Dose and Dosage 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.

The adverse reactions listed below were reported in ketorolac tromethamine clinical efficacy trials. In these trials patients (N=660) received either single 30 mg doses (N=151) or multiple 30 mg doses (N=509) over a time period of 5 days or less for pain resulting from surgery. These reactions may or may not be drug related.

**Table 1: Most Common Clinical Trial Adverse Drug Reactions (10 to 13%, 4 to 9% and 2 to 3%)**

Body System	Incidence	Adverse Reaction
Nervous System	10-13%	Somnolence
	4-9%	Headache
	2-3%	Sweating, dizziness
Digestive System	10-13%	Nausea
	4-9%	Vomiting
Injection Site	4-9%	Injection site pain
Cardiovascular System	2-3%	Vasodilation

## 8.3 Less Common Clinical Trial Adverse Reactions

**Table 2: Less Common Clinical Trial Adverse Drug Reactions ( $\leq 1\%$ )**

Nervous system	insomnia, increased dry mouth, abnormal dreams, anxiety, depression, paraesthesia, nervousness, paranoid reaction, speech disorder, euphoria, libido increased, excessive thirst, inability to concentrate, stimulation
Digestive system	flatulence, anorexia, constipation, diarrhea, dyspepsia, gastrointestinal fullness, gastrointestinal haemorrhage, gastrointestinal pain, melena, sore throat, liver function abnormalities, rectal bleeding, stomatitis
Cardiovascular system:	hypertension, chest pain, tachycardia, haemorrhage, palpitation, pulmonary embolus, syncope, ventricular tachycardia, pallor, flushing
Injection site	injection site reaction
Body as a Whole	asthenia, fever, back pain, chills, pain, neck pain

<b>Special senses</b>	taste perversion, tinnitus, blurred vision, diplopia, retinal hemorrhage
<b>Musculo-skeletal system</b>	myalgia, twitching
<b>Respiratory system</b>	asthma, cough increased, dyspnea, epistaxis, hiccup, rhinitis
<b>Skin and appendages</b>	pruritus, rash, subcutaneous hematoma, skin disorder
<b>Urogenital system</b>	dysuria, urinary retention, oliguria, increased urinary frequency, vaginitis
<b>Metabolic/nutritional disorders</b>	edema, hypokalemia, hypovolemia
<b>Hematologic and lymphatic system</b>	anemia, coagulation disorder, purpura

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

##### **Abnormal Haematologic and Clinical Chemistry 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 ketorolac tromethamine (tablets and injection):

**Blood and lymphatic system disorder:** postoperative wound haemorrhage, rarely requiring blood transfusion (see [7 WARNINGS AND PRECAUTIONS](#)), thrombocytopenia, epistaxis, leukopenia, hematomata, increased bleeding time.

**Cardiac disorders:** pulmonary edema, hypotension, flushing, bradycardia.

**Infections and infestations:** infection.

**Gastrointestinal disorders:** gastrointestinal hemorrhage, peptic ulceration, gastrointestinal perforation, pancreatitis, melena, esophagitis, hematemesis, vomiting, ulcerative stomatitis.

**Hepatobiliary disorders:** Abnormal liver function tests, jaundice, hepatitis, liver failure, cholestatic jaundice.

**Nervous system disorders:** Convulsions, abnormal dreams, hallucinations, hyperkinesia,

hearing loss, aseptic meningitis, extrapyramidal symptoms, psychotic reactions.

**Renal and urinary disorders:** acute renal failure, flank pain with or without haematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome, urinary retention, interstitial nephritis, nephrotic syndrome, haematuria, raised serum urea and creatinine.

**Reproductive system and breast disorders:** infertility.

**Respiratory, thoracic and mediastinal disorders:** bronchospasm, laryngeal edema, asthma, hypotension, flushing, rash, anaphylaxis, angioedema and anaphylactoid reactions. Such reactions have occurred in patients with no prior history of hypersensitivity.

**Skin and subcutaneous tissue disorders:** Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash, urticaria, alopecia, erythema multiforme, epidermal necrolysis, photosensitive dermatitis, erythema nodosum.

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

#### Serious Drug Interactions

- **NSAIDs:** APO-KETOROLAC Injectable is contraindicated in patients currently receiving acetylsalicylic acid (ASA) or NSAIDs because of the cumulative risk of serious NSAID related side effects. See [2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions](#).
- **Pentoxifylline:** The concomitant use of APO-KETOROLAC Injectable and pentoxifylline is contraindicated due to the increased risk of bleeding. See [2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions](#).
- **Probenacid:** The concomitant use of APO-KETOROLAC Injectable and probenacid 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 APO-KETOROLAC Injectable. 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

**Table 3 - Established or Potential Drug-Drug Interactions**

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) or other NSAIDs:	CT	<ul style="list-style-type: none"> <li>• The concomitant use of ketorolac tromethamine 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.</li> <li>• 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.</li> <li>• Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects</li> </ul>	<ul style="list-style-type: none"> <li>• Concomitant use of APO-KETOROLAC Injectible and analgesic doses of ASA or other NSAIDs is not recommended because of the increased risk of bleeding. See <a href="#">Z WARNINGS AND PRECAUTIONS</a></li> </ul>

Proper/Common name	Source of Evidence	Effect	Clinical comment
		<p>of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1. <i>In vitro</i> 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.</p>	
<p>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers</p>	<p>T</p>	<ul style="list-style-type: none"> <li>• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol).</li> <li>• In patients who are elderly, volume-depleted (including those on diuretic therapy), or have RI, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure</li> </ul>	<ul style="list-style-type: none"> <li>• 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 <a href="#">7 WARNINGS AND PRECAUTIONS.</a></li> </ul>



Proper/Common name	Source of Evidence	Effect	Clinical comment
		and hyperkalemia. These effects are usually reversible.	
Antacids	N/A	<ul style="list-style-type: none"> <li>There is no definitive evidence that the concomitant administration of histamine H<sub>2</sub>-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.</li> </ul>	<ul style="list-style-type: none"> <li>Concomitant administration is not recommended.</li> </ul>
Anti-coagulants	CT	<ul style="list-style-type: none"> <li>Ketorolac tromethamine and anticoagulants such as warfarin have a synergistic effect on bleeding.</li> <li>The concomitant use of ketorolac tromethamine and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.</li> </ul>	Anticoagulation/INR should be monitored and warfarin dosage adjustments. See <a href="#">Z WARNINGS AND PRECAUTIONS: Haematologic, Anticoagulants</a>
Anti-platelets Agents (including ASA)	CT	<ul style="list-style-type: none"> <li>There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as</li> </ul>	Monitor patients for signs of bleeding. See <a href="#">Anti-platelet Effects</a>

Proper/Common name	Source of Evidence	Effect	Clinical comment
		ketorolac tromethamine	
Cyclosporin and Tacrolimus	T	<ul style="list-style-type: none"> <li>Inhibition of renal prostaglandin activity by NSAIDs may increase the nephrotoxic effect of cyclosporin or tacrolimus.</li> </ul>	<ul style="list-style-type: none"> <li>Patients should be monitored for necessary dosage adjustment.</li> <li>Monitor patients for signs of worsening renal function. See <a href="#">7 WARNINGS AND PRECAUTIONS: Renal</a></li> </ul>
Digoxin	C	<ul style="list-style-type: none"> <li>The concomitant use of ketorolac tromethamine 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.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor serum digoxin levels.</li> </ul>
Diuretics	CT	<ul style="list-style-type: none"> <li>Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.</li> <li>This effect has been attributed to the NSAID inhibition of renal prostaglandin</li> </ul>	<ul style="list-style-type: none"> <li>Observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. See <a href="#">7 WARNINGS AND PRECAUTIONS</a></li> </ul>

Proper/Common name	Source of Evidence	Effect	Clinical comment
		<p>synthesis.</p> <ul style="list-style-type: none"> <li>• 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.</li> </ul>	
Glucocorticoids	CT	<ul style="list-style-type: none"> <li>• The concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding, especially in older (&gt;65 years of age) patients.</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor patients particularly those over 65 years of age for signs of bleeding. See <a href="#">7 WARNINGS AND PRECAUTIONS.</a></li> </ul>
Lithium	CT	<ul style="list-style-type: none"> <li>• NSAIDs have produced elevations in plasma lithium levels and reductions in 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</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor patients for plasma lithium concentrations when stopping or starting a NSAID</li> </ul>

Proper/Common name	Source of Evidence	Effect	Clinical comment
		during therapy with ketorolac tromethamine have been reported.	
Methotrexate	N/A	<ul style="list-style-type: none"> <li>Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, cytopenia, renal dysfunction).</li> </ul>	<ul style="list-style-type: none"> <li>Monitor patients for methotrexate toxicity. Blood cell count and the renal function should be monitored</li> </ul>
Pentoxifylline		<ul style="list-style-type: none"> <li>When ketorolac tromethamine is administered concurrently with pentoxifylline, there is an increased tendency to bleeding.</li> </ul>	<ul style="list-style-type: none"> <li>The concomitant use of APO-KETOROLAC Injectable and pentoxifylline is contraindicated</li> </ul>
Probenecid	CT	<ul style="list-style-type: none"> <li>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 (approximately three-fold increase) and terminal half-life (approximately two-fold increase).</li> </ul>	<ul style="list-style-type: none"> <li>The concomitant use of APO-KETOROLAC Injectable and probenecid is contraindicated.</li> </ul>
Selective serotonin reuptake inhibitors (SSRIs)	C	<ul style="list-style-type: none"> <li>Concomitant administration of NSAIDs and SSRIs may increase the</li> </ul>	<ul style="list-style-type: none"> <li>Monitor patients for signs of bleeding. See <a href="#">7 WARNINGS AND PRECAUTIONS</a></li> </ul>

Proper/Common name	Source of Evidence	Effect	Clinical comment
		risk of gastrointestinal ulceration and bleeding).	

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

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.

### 10.1 Mechanism of Action

APO-KETOROLAC Injectable (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.

### 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 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 4 below).

The parenteral administration of ketorolac tromethamine has not been demonstrated to affect the haemodynamics of anaesthetized 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. 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 of humans. 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

- **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:** See [7.1.1 Pregnant 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 4: The influence of age, liver and kidney function on the clearance and terminal half-life of ketorolac tromethamine injection (IM)<sup>1</sup> and ORAL<sup>2</sup>**

Types of Subjects	Total Clearance (in L/h/kg) <sup>3</sup>		Terminal Half Life (in hours)	
	IM MEAN (range)	ORAL MEAN (range)	IM MEAN (range)	ORAL MEAN (range)
<b>Normal Subjects</b> IM (n=54) Oral (n=77)	0.023 (0.010-0.046)	0.025 (0.013-0.050)	5.3 (3.5-9.2)	5.3 (2.4-9.0)
<b>Healthy Elderly Subjects</b> IM (n=13) Oral (n=12) (mean age = 72, range = 65-78)	0.019 (0.013-0.034)	0.024 (0.018-0.034)	7.0 (4.7-8.6)	6.1 (4.3-7.6)
<b>Patients with Hepatic Dysfunction</b> IM and Oral (n=13)	0.029 (0.013-0.066)	0.033 (0.019-0.051)	5.4 (2.2-6.9)	4.5 (1.6-7.6)
<b>Patients with Renal Impairment</b> IM and Oral (n=9) (serum creatinine 1.9-5.0 mg/dL)	0.014 (0.007-0.043)	0.016 (0.007-0.052)	10.3 (8.1-15.7)	10.8 (3.4-18.9)

Types of Subjects	Total Clearance (in L/h/kg) <sup>3</sup>		Terminal Half Life (in hours)	
	IM MEAN (range)	ORAL MEAN (range)	IM MEAN (range)	ORAL MEAN (range)
<b>Renal Dialysis Patients</b> IM (n=9)	0.016 (0.003-0.036)	N/A	13.6 (8.0-39.1)	N/A

<sup>1</sup> Estimated from 30 mg single IM doses of ketorolac tromethamine  
<sup>2</sup> Estimated from 10 mg single oral doses of ketorolac tromethamine  
<sup>3</sup> Litres/hour/kilogram

## 11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C. Protect from light. Single use vials. Discard unused portion. Keep out of reach and sight of children.

## 12 SPECIAL HANDLING INSTRUCTIONS

N/A



## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

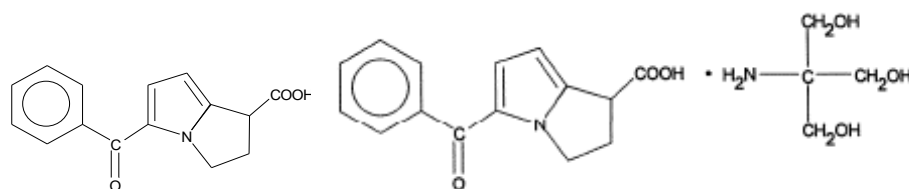
#### Drug Substance

Proper name: Ketorolac tromethamine

Chemical name: ( $\pm$ )-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid,  
2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Molecular formula and molecular mass:  $C_{19}H_{24}N_2O_6$  376.41 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, ethyl acetate, dioxane, hexane, butanol and acetonitrile. The pH of a 1% (w/v) solution in distilled water is 5.7 to 6.7. Its melting point is about 162°C with decomposition.

### 14 CLINICAL TRIALS

No data available.

### 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 <sub>50</sub> (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 haemoglobin and haematocrit 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.

## **Subchronic 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.

Haematologic parameters measured revealed decreased haemoglobin and haematocrit 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 haematologic and pathologic effects at all dose levels. Clinically, a few isolated instances of dark coloured urine, vomiting and dark colored feces (fecal blood) were seen in all dose groups but not in controls. There was a slight decrease in haemoglobin and haematocrit 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 haemorrhage 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 haematologic changes occurred in some treated animals. Gross and/or microscopic examinations of the injection sites revealed focal haemorrhage, 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, haemoglobin, haematocrit, mean corpuscular haemoglobin and haemoglobin 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.

### **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.

#### **Genotoxicity:**

#### **Mutagenicity**

*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.

## **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 mid-gestation 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 mid-gestation 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.

#### **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.

#### **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 embryoletality 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.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1 Toradol® IM, Solution, 10 mg/mL, submission control 256960, Product Monograph, Atnahs Pharma UK Limited. (APR 13, 2022)

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### <sup>Pr</sup>APO-KETOROLAC Injectable

#### Ketorolac Tromethamine Injection

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

#### Serious Warnings and Precautions

##### Heart and blood vessel problems:

- APO-KETOROLAC Injectable can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take APO-KETOROLAC Injectable 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:

- APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) **only** take APO-KETOROLAC Injectable if you are told to do so by your healthcare professional.
- Medicines like APO-KETOROLAC Injectable may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe APO-KETOROLAC Injectable during this time.
- Tell your healthcare professional **right away** if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with APO-KETOROLAC Injectable.

### **What is APO-KETOROLAC Injectable used for?**

APO-KETOROLAC Injectable is used in adults to relieve moderate to severe pain, usually after surgery.

APO-KETOROLAC Injectable will be given to you in a hospital or medical office for no more than 2 days.

### **How does APO-KETOROLAC Injectable work?**

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

### **What are the ingredients in APO-KETOROLAC Injectable?**

Medicinal ingredients: ketorolac tromethamine

Non-medicinal ingredients: alcohol, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

### **APO-KETOROLAC Injectable comes in the following dosage forms:**

APO-KETOROLAC Injectable is available as solution for intramuscular injection (30 mg/mL).

### **Do not use APO-KETOROLAC Injectable if you:**

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

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-KETOROLAC Injectable. 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 asthma.
- have other bleeding or blood problems.
- have immune system problems.
- are pregnant, planning on becoming or become pregnant while taking APO-KETOROLAC Injectable.
- are taking any other medicines.

**Other warnings you should know about:**

**APO-KETOROLAC Injectable may cause serious side effects, including:**

- **Blood and bleeding problems:**
  - APO-KETOROLAC Injectable can cause blood problems, bleeding and prolonged bleeding.
  - Taking APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable. These skin problems most often happen during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment. APO-KETOROLAC Injectable 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:** APO-KETOROLAC Injectable 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.

**Wound bleeding:** APO-KETOROLAC Injectable may cause your wound to bleed after surgery. Tell your healthcare professional if you notice painful swelling, bruising, lumps or active bleeding from your wound after you are given APO-KETOROLAC Injectable.

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

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

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

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

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

- Check your blood pressure.
- Check your eyes. APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable 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 APO-KETOROLAC Injectable:**

- 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, ASA, clopidogrel, heparin, and dextrans
- cyclosporin, used to lower the risk of organ transplant rejection
- methotrexate, used to treat different cancers
- digoxin, used to treat heart disorders
- corticosteroids (including glucocorticoids such as prednisone), used to treat inflammation
- alcohol

### **How to take APO-KETOROLAC Injectable:**

- APO-KETOROLAC Injectable will be given to you by a healthcare professional in a hospital or medical office. It is usually given for no more than 2 days.
- The dose given to you will depend on the severity of your pain. Your healthcare professional will give you the lowest dose possible for your treatment for the shortest time needed.
- Tell your healthcare professional if you notice any side effects while receiving this medicine. They may change your dose depending on your response to APO-KETOROLAC Injectable.
- Your healthcare professional may prescribe you ketorolac tromethamine tablets to take by mouth during or following your treatment with APO-KETOROLAC Injectable. Take them as directed by your healthcare professional.

### Usual dose:

Your healthcare professional will decide the right dose for you.

### Overdose:

Signs of an overdose with APO-KETOROLAC Injectable 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 been given too much APO-KETOROLAC Injectable, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

### What are possible side effects from using APO-KETOROLAC Injectable?

These are not all the possible side effects you may have when taking APO-KETOROLAC Injectable. 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
- Inability to concentrate, anxiety, nervousness
- Thirst, dry mouth, sore throat, changes in tastes
- Bruises, rash
- Muscle pain/twitching
- Mouth sores
- Increased sweating
- Pain at injection site

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	
<b>COMMON</b>			
<b>Gastrointestinal (GI) problems</b> (bleeding, blockage, holes, ulcers)		√	

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	
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			
<b>Hypertension</b> (high blood pressure): fatigue, dizziness or fainting, chest pain	√		
<b>UNCOMMON</b>			
<b>Anaphylaxis/hypersensitivity</b> (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock			√
<b>Aseptic meningitis</b> (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		√	
<b>Blood problems</b> (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		√	
<b>Congestive heart failure</b> (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			√
<b>Cystitis</b> (bladder infection): increased need to urinate, pain in		√	



Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating			
<b>Depression</b> (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.		√	
<b>Kidney disorder/problems (including kidney failure):</b> 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)		√	
<b>Liver problems (including hepatitis, liver failure, cholestasis):</b> yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		√	
<b>Lung problems, asthma:</b> increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			√
<b>Myocardial infarction</b> (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			√

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	
heartbeat.			
<b>Stroke</b> (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			√
<b>Tinnitus</b> (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		√	
<b>Vertigo</b> (a sense of severe spinning dizziness, lightheadedness)		√	
<b>RARE</b>			
<b>Serious Skin Reactions:</b> fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, hives, red or dry itchy skin, purple or red spots on skin			√

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

### Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health->

[products/medeffect-canada/adverse-reaction-reporting.html](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/medeffect-canada/adverse-reaction-reporting.html)) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

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

**Storage:**

- Store APO-KETOROLAC Injectable at room temperature (15°C to 30°C). Protect from light. Single use vials. Discard unused portion.
- Keep out of reach and sight of children.

**If you want more information about APO-KETOROLAC Injectable:**

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

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

Last Revised: March 7, 2023