PRODUCT MONOGRAPH

Ketorolac Tromethamine Injection, USP

30 mg/mL

Non-Steroidal Anti-Inflammatory Analgesic Agent

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Date of Preparation: March 5, 2015

Control No.: 181764
Ketorolac tromethamine Injection, USP

Therapeutic Classification
Non-steroidal anti-inflammatory - Analgesic agent

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity mediated by peripheral effects. Ketorolac inhibits the synthesis of prostaglandins through inhibition of the cyclooxygenase enzyme system. At analgesic doses, it has minimal anti-inflammatory and antipyretic activity.

Pain relief is comparable following the administration of ketorolac by intramuscular or oral routes. The peak analgesic effect occurs at 2 - 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.

Ketorolac tromethamine is rapidly and completely absorbed when administered by either the oral or the intramuscular route. 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 µg/mL occur at 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 1).

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.

More than 99% of the ketorolac in plasma is protein bound over a wide concentration range.

The parenteral administration of ketorolac tromethamine has not been demonstrated to affect the hemodynamics of anaesthetized patients.
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<td>Renal Dialysis Patients i.m. (n = 9)</td>
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1 Estimated from 30 mg single i.m. doses of ketorolac tromethamine
2 Estimated from 10 mg single oral doses of ketorolac tromethamine
3 Litres/hour/kilogram
INDICATIONS

Intramuscular injection of Ketorolac Tromethamine Injection, USP is indicated for the short-term management (not to exceed 2 days) of moderate to severe acute pain, including pain following major abdominal, orthopedic and gynecological operative procedures. The total duration of combined intramuscular and oral treatment should not exceed 5 days.

CONTRAINDICATIONS

**Hypersensitivity**
Like other non-steroidal anti-inflammatory drugs, ketorolac tromethamine has been associated with hypersensitivity reactions. Ketorolac tromethamine should not be used when there is a known or suspected hypersensitivity to the drug and should be discontinued in patients who develop symptoms of hypersensitivity during therapy. Because of the possibility of cross-sensitivity, ketorolac tromethamine should not be used in patients with the complete or partial syndrome of nasal polyps, angioedema, bronchospastic reactivity (e.g., asthma) or other allergic manifestations to acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs. Severe and fatal anaphylactoid reactions have occurred in such individuals.

**Gastrointestinal**
Ketorolac tromethamine should not be used in patients with suspected or confirmed peptic ulcer disease, gastrointestinal bleeding or perforation, or active inflammatory disease of the gastrointestinal system or in patients who have a history of these disorders. Severe and fatal reactions have occurred in such individuals.

**Renal Impairment**
Ketorolac tromethamine is contraindicated in patients with moderate to severe renal impairment or in patients at risk for renal failure due to volume depletion.

**Hemorrhagic Risk**
Ketorolac tromethamine is contraindicated immediately before any major surgery, and is contraindicated intraoperatively when hemostasis is critical because of the increased risk of bleeding. Ketorolac tromethamine is also contraindicated in patients with coagulation disorders, postoperative patients with high hemorrhagic risk or incomplete hemostasis, and in patients with suspected or confirmed cerebrovascular bleeding.
Obstetrics
Ketorolac tromethamine is contraindicated in labour and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.

Neuraxial Administration
Ketorolac Tromethamine Injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.

Concomitant Medications
Ketorolac tromethamine is contraindicated in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events. The concomitant use of ketorolac tromethamine and probenecid is also contraindicated.

WARNINGS
The long-term administration of ketorolac tromethamine is not recommended as the incidence of side-effects increases with the duration of treatment (see INDICATIONS and DOSAGE AND ADMINISTRATION).

The most serious risks associated with NSAIDs including ketorolac tromethamine are:

Gastrointestinal Ulcerations, Bleeding and Perforation
Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, during therapy with non-steroidal anti-inflammatory drugs. The incidence of gastrointestinal complications increases with dosage and duration of treatment. Elderly and debilitated patients are more susceptible to these complications.

To date, studies with NSAIDs have not identified any subset of patients not at risk for developing peptic ulceration and bleeding.

Postmarketing 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 the aged population.
THE LONG-TERM USE OF KETOROLAC TROMETHAMINE IS NOT RECOMMENDED.

**Renal Toxicity**
The following renal abnormalities have been associated with ketorolac tromethamine and other drugs that inhibit renal prostaglandin biosynthesis: acute renal failure, nephrotic syndrome, interstitial nephritis, renal papillary necrosis. Elevations of blood urea nitrogen (BUN) and creatinine have been reported in clinical trials with ketorolac tromethamine. Ketorolac tromethamine is contraindicated in patients with moderate to severe renal impairment.

Hypovolemia should be corrected before treatment with ketorolac tromethamine is initiated. Patients who are volume depleted may be dependent on renal prostaglandin production to maintain renal perfusion and, therefore, glomerular filtration rate. In such patients, the use of drugs which inhibit prostaglandin synthesis has been associated with further decreases in renal blood flow and may precipitate acute renal failure. Predisposing factors include dehydration (e.g. as a result of extreme exercise, vomiting or diarrhea associated with the loss of at least 5 to 10% of total body weight, unreplenished blood loss of approximately 500 mL), sepsis, impaired renal function, heart failure, liver dysfunction, diuretic therapy, and advanced age. Caution is advised if ketorolac tromethamine is used in such circumstances. Close monitoring of urine output, serum urea and serum creatinine is recommended until renal function recovers.

**Fluid Retention and Edema**
Fluid retention, edema, NaCl retention, oliguria, elevations of serum urea nitrogen and creatinine have been observed in patients treated with ketorolac tromethamine. Therefore, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be considered. Ketorolac tromethamine should be used with caution in patients with cardiac decompensation, hypertension or other conditions which cause a predisposition to fluid retention.

**Hemorrhage**
Postoperative hematomas and other symptoms of wound bleeding have been reported in association with the perioperative use of intramuscular ketorolac tromethamine. Ketorolac tromethamine is contraindicated in patients who have coagulation disorders. If ketorolac tromethamine is to be administered to patients who are receiving drug therapy that interferes with hemostasis, careful observation is advised.

Use of ketorolac tromethamine in patients who are receiving therapy that affects hemostasis should be undertaken with caution, including close monitoring. The concurrent use of ketorolac tromethamine and prophylactic, low dose heparin (2500 - 5000 units q12h), warfarin and dextrans may also be associated with an increased risk of bleeding (see **DRUG INTERACTIONS**).
In patients receiving anticoagulants, the risk of intramuscular hematoma formation from ketorolac tromethamine injections is increased.

**Hypersensitivity Reactions**
The possibility of severe or fatal hypersensitivity reactions should be considered, even for patients with no known history of previous exposure or hypersensitivity to ketorolac tromethamine or other NSAIDs. Counteractive measures must be available when administering the first dose of ketorolac tromethamine. As with other NSAIDs, patients should be questioned for history of allergy to NSAIDs or ASA or for the syndrome consisting of nasal polyps, ASA allergy and asthma before being prescribed ketorolac tromethamine. Asthmatic patients with triad asthma (the syndrome of nasal polyps, asthma and hypersensitivity to ASA or other NSAIDs) may be at particular risk for severe hypersensitivity reactions.

**Use in Pregnancy and Lactation**
The administration of ketorolac tromethamine is not recommended during pregnancy or lactation. After 1 day at 10 mg q.i.d. oral dosing, ketorolac tromethamine has been detected in the milk of lactating women at a maximum concentration of 7.9 ng/mL.

**Use in Children**
Safety and efficacy in children have not been established. Therefore, ketorolac tromethamine is not recommended for use in children under age 16.

**Use in the Elderly**
Because ketorolac is cleared somewhat more slowly by the elderly (see **PHARMACOLOGY, Pharmacokinetics**) who are also more sensitive to the gastrointestinal and renal effects of NSAIDs, (see **WARNINGS and PRECAUTIONS**), extra caution and the lowest effective dose (see **DOSAGE AND ADMINISTRATION**) should be used.

**PRECAUTIONS**

Physicians should be alert to the pharmacologic similarity of ketorolac tromethamine to other non-steroidal anti-inflammatory drugs that inhibit cyclooxygenase.

**Gastrointestinal Effects**
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.
Patients taking any NSAID including ketorolac tromethamine should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur at any time during the treatment. If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding occurs, ketorolac tromethamine should be discontinued and appropriate treatment instituted with close patient monitoring.

**Hepatic Effects**
Caution should be observed if ketorolac tromethamine is to be used in patients with impaired hepatic function, or a history of liver disease. Treatment with ketorolac tromethamine may cause elevations of liver enzymes, and in patients with pre-existing liver dysfunction, it may lead to the development of a more severe hepatic reaction. Meaningful elevations (greater than 3 times normal) of serum transaminases [glutamate pyruvate (SGPT or ALT) and glutamic oxaloacetic (SGOT or AST], occurred in controlled clinical trials in less than 1% of patients. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ketorolac tromethamine should be discontinued. Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac tromethamine clearance. Studies in patients with active hepatitis or cholestasis have not been performed.

**Hematologic Effects**
Ketorolac tromethamine inhibits platelet function and may prolong bleeding time. It does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Unlike the prolonged effects from ASA the inhibition of platelet function by ketorolac tromethamine is normalized within 24 to 48 hours after the drug is discontinued.

Blood dyscrasias associated with the use of NSAIDs are rare, but could occur with severe consequences.

**Infection**
In common with other non-steroidal anti-inflammatory drugs, ketorolac tromethamine may mask the usual signs of infection.


**DRUG INTERACTIONS**

**Protein Binding**

Ketorolac tromethamine is highly bound to human plasma protein (mean 99.2%) and binding is independent of concentration. As ketorolac tromethamine is a highly potent drug and present in low concentrations in plasma, it would not be expected to displace other protein-bound drugs significantly. Therapeutic concentrations of digoxin, warfarin, acetaminophen, phenytoin, and tolbutamide did not alter ketorolac tromethamine protein binding.

**Anticoagulant Therapy**

Prothrombin time should be carefully monitored in all patients receiving oral anticoagulant therapy concomitantly with ketorolac tromethamine. Ketorolac tromethamine given with two doses of 5000 U of heparin to 11 healthy volunteers, resulted in a mean template bleeding time of 6.4 min (3.2 - 11.4 min) compared to a mean of 6.0 min (3.4 - 7.5 min) for heparin alone and 5.1 min (3.5 - 8.5 min) 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 µg/mL.

**Digoxin**

Ketorolac tromethamine does not alter digoxin protein binding.

**Salicylates**

*In vitro* studies indicated that, at therapeutic concentrations of salicylates (300 µg/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.

**Enzyme Induction**

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

**Probenecid**

Concomitant administration of ketorolac tromethamine and probenecid results in the decreased clearance of ketorolac and a significant increase in ketorolac plasma levels (approximately three-fold increase) and terminal half-life (approximately two-fold increase). The concomitant use of Ketorolac Tromethamine Injection and probenecid is, therefore, contraindicated.
Furosemide
Ketorolac tromethamine reduces the diuretic response to furosemide by approximately 20% in normovolemic subjects.

Lithium
Some NSAIDs have been reported to inhibit renal lithium clearance, leading to an increase in plasma lithium concentrations and potential lithium toxicity. The effect of ketorolac tromethamine on lithium plasma levels has not been studied.

Methotrexate
The concomitant administration of methotrexate and some NSAIDs has been reported to reduce the clearance of methotrexate, thus enhancing its toxicity. The effect of ketorolac tromethamine on methotrexate clearance has not been studied.

ACE Inhibitors
Concomitant use of ACE inhibitors and other NSAIDs may increase the risk of renal impairment, particularly in volume depleted patients.

Morphine
Intramuscular ketorolac tromethamine has been administered concurrently with morphine in several clinical trials of postoperative pain without evidence of adverse interactions.

ADVERSE EVENTS

The adverse reactions listed below were reported in Ketorolac Tromethamine Injection 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.

Incidence Between 10 and 13%
Nervous system: somnolence
Digestive system: nausea

Incidence Between 4 and 9%
Nervous system: headache
Digestive system: vomiting
Injection site: injection site pain
Incidence Between 2 and 3%
Nervous system: sweating, dizziness
Cardiovascular system: vasodilation

Incidence 1% or Less:
Nervous system: insomnia, increased dry mouth, abnormal dreams, anxiety, depression, paresthesia, nervousness, paranoid reaction, speech disorder, euphoria, libido increased, excessive thirst, inability to concentrate, stimulation
Digestive system: flatulence, anorexia, constipation, diarrhea, dyspepsia, gastrointestinal fullness, gastrointestinal hemorrhage, gastrointestinal pain, melena, sore throat, liver function abnormalities, rectal bleeding, stomatitis
Cardiovascular system: hypertension, chest pain, tachycardia, hemorrhage, 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
Special senses: taste perversion, tinnitus, blurred vision, diplopia, retinal hemorrhage
Musculo-skeletal system: myalgia, twitching
Respiratory system: asthma, cough increased, dyspnea, epistaxis, hiccup, rhinitis
Skin and appendages: pruritus, rash, subcutaneous hematoma, skin disorder
Urogenital system: dysuria, urinary retention, oliguria, increased urinary frequency, vaginitis
Metabolic/nutritional disorders: edema, hypokalemia, hypovolemia
Hemic and lymphatic system: anemia, coagulation disorder, purpura

Postmarketing Experience
The following postmarketing adverse experiences have been reported for patients who have received either the oral or injectable formulation of ketorolac tromethamine:

Renal events: acute renal failure, flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome, urinary retention.
Hypersensitivity reactions: bronchospasm, laryngeal edema, asthma, hypotension, flushing, rash, anaphylaxis, and anaphylactoid reactions. Such reactions have occurred in patients with no prior history of hypersensitivity.
Gastrointestinal events: gastrointestinal hemorrhage, peptic ulceration, gastrointestinal perforation, pancreatitis, melena.
Hematologic events: postoperative wound hemorrhage, rarely requiring blood transfusion (see PRECAUTIONS), thrombocytopenia, epistaxis, leukopenia
Central nervous system: convulsions, abnormal dreams, hallucinations, hyperkinesia, hearing loss, aseptic
meningitis, extrapyramidal symptoms.

**Hepatic events:** hepatitis, liver failure, cholestatic jaundice

**Cardiovascular:** pulmonary edema, hypotension, flushing

**Dermatology:** Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash, urticaria.

**Body as whole:** infection

**OVERDOSAGE**

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. Metabolic acidosis has been reported following intentional overdosage. Single oral doses of 200 mg have been administered to patients with no apparent serious side effects. Dialysis does not appreciably clear ketorolac from the blood stream.

**DOSAGE AND ADMINISTRATION**

**Adults**

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

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

The administration of Ketorolac Tromethamine Injection, USP should be limited to short-term therapy (not over 2 days). The total daily dose should not exceed 120 mg because the risk of toxicity appears to increase with longer use at recommended doses (see **WARNINGS** and **PRECAUTIONS**). The administration of continuous multiple daily doses of Ketorolac Tromethamine Injection has not been extensively studied. There has been limited experience with intramuscular dosing for more than 3 days since the vast majority of patients have transferred to oral medication or no longer required analgesic therapy after this time. If supplementary analgesia is required, a concomitant low dose of opiate can be used.
**Patients Under 50 kg, Over Age 65 years, or With Less Severe Pain at Baseline**

**Parenteral:** The lower end of the dosage range is recommended. The initial dose should be 10 mg. The total daily dose of Ketorolac Tromethamine Injection in the elderly should not exceed 60 mg.

**Impaired Renal Function**
Ketorolac tromethamine is not recommended for patients with moderate to severe renal impairment.

**Conversion from Parenteral to Oral Therapy**
Ketorolac tromethamine tablets may be used either as monotherapy or as follow-on therapy to parenteral ketorolac. 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. Ketorolac Tromethamine Injection should be replaced by an oral analgesic as soon as feasible.

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

Parenteral drug products should be inspected visually for particulate material and discoloration prior to use. Ketorolac tromethamine is a Prescription drug.
PHARMACEUTICAL INFORMATION

Structural formula:

![Structural formula image]

Molecular formula: $\text{C}_{15}\text{H}_{13}\text{NO}_3 \cdot \text{C}_4\text{H}_{11}\text{NO}_3$

Molecular weight: 376.40

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

Physical Form: Ketorolac tromethamine is a white to off-white crystalline powder.

Solubility: It is freely soluble in water and methanol; slightly soluble in alcohol, in dehydrated alcohol, in tetrahydrofuran; and practically insoluble in acetone, in dichloromethane, in toluene, in ethylacetate, in dioxane, in hexane, in butyl alcohol and in acetonitrile.

pKa and pH: The pKa is 3.46 and the pH of a 1% (w/v) solution in carbon dioxide free, purified water is 5.7 - 6.7.

Melting Point: Melts at about 162 °C with decomposition.

Composition
Ketorolac Tromethamine Injection, USP 30 mg/mL, each mL contains: ketorolac tromethamine 30 mg, and as non-medicinal ingredients: alcohol USP 100 mg, citric acid 1 mg, sodium chloride 4.35 mg for isotonicity, and sodium hydroxide and/or hydrochloric acid for pH adjustment, in sterile water for injection.

STABILITY AND STORAGE RECOMMENDATIONS
Store between 15 °C and 30 °C, protect from light and freezing.
AVAILABILITY OF DOSAGE FORMS

Ketorolac Tromethamine Injection, USP is available as follows:

C160201  30 mg/mL ketorolac tromethamine, 1 mL fill in a 2 mL single-dose vial with latex free stopper with a mist gray coloured flip-off cap. Available in packages of 25 vials.

C160202  30 mg/mL ketorolac tromethamine, 2 mL fill in a 2 mL single-dose vial with latex free stopper with a purple coloured flip-off cap. Available in packages of 25 vials.
PHARMACOLOGY

Animal Pharmacology

Analgesic Properties:
Ketorolac is a potent orally active analgesic agent in tests utilizing an underlying inflammatory state. In mice, given oral or subcutaneous doses ranging from 0.05 - 2.25 mg/kg, the compound was 250 - 350 times more potent than ASA in inhibiting phenylquinone-induced writhing. Using a similar test in rats which received 0.03 - 1.0 mg/kg p.o., ketorolac was 180 times as potent as aspirin in inhibiting the writhing response.

In rats having adjuvant-induced arthritis, ketorolac p.o. was 400 - 800 times more potent than aspirin and twice as potent as naproxen in alleviating pain. The compound also significantly increased the pain threshold in yeast-inflamed paws of rats which were compressed at a constant rate of pressure (Randall-Selitto Test), its potency being 3 to 10 times that of naproxen.

The fact that ketorolac does not increase the pain threshold of the non-inflamed paw and does not exhibit analgesic activity in the mouse hot plate test indicates that it is not a morphine like compound.

Anti-inflammatory Properties:
Ketorolac displayed anti-inflammatory properties when tested in classical rat models to test intrinsic anti-inflammatory actions. The free acid form of the compound had approximately 36 times the anti-inflammatory potency of phenylbutazone, while the tromethamine salt was 118 times as active as phenylbutazone in inhibiting carrageenin-induced paw inflammation when administered orally. This difference in potency is due to the compound.

Ketorolac was weakly effective in inhibiting the development of ultraviolet-induced erythema when applied topically at a dose of 1 mg to guinea pigs. In the rat, however, topical application at dose levels of 0.01 and 0.1 mg/rat, was very effective in suppressing the heat induced local inflammatory reaction.

When administered to rats at a dose of 2 mg/kg/day p.o., for 6 days, ketorolac did not produce thymic involution. This indicates that the anti-inflammatory activity is not due to intrinsic corticosteroid activity in the molecule nor due to the stimulation of endogenous corticosteroid production. These findings were further confirmed by the dose-related anti-inflammatory activity in adrenalectomized rats.
**Antipyretic Properties:**
When administered orally to yeast-infected rats in doses ranging from 0.1 - 2.7 mg/kg, ketorolac had 20 times the antipyretic potency of aspirin.

**Prostaglandin Inhibition:**
There is substantial evidence in the literature to suggest that the anti-inflammatory, analgesic and antipyretic activities of non-steroidal anti-inflammatory drugs (NSAIDs) are due to their ability to inhibit prostaglandin biosynthesis.

Ketorolac, like other NSAIDs, inhibited the prostaglandin synthetase activity in bovine seminal vesicle microsomes, rabbit renal medullary microsomes, and human platelet microsomes, having substantially greater potency (1.0 to 5.3 times) than indomethacin.

**Platelet Effects:**
In *in vitro* studies, ketorolac was 37 times as active as aspirin in inhibiting aggregation of human platelets induced by collagen and 28 times more potent than aspirin in inhibiting arachidonic acid-induced platelet aggregation. However, ketorolac did not inhibit the primary phase of adenosine diphosphate-induced aggregation nor the aggregation elicited by thromboxane A2.

**Central Nervous System Effects:**
The acute intraperitoneal administration of ketorolac to mice had minimal behavioral effects at doses up to 300 mg/kg. Above this dose level, depression of normal behavior was seen.

No appreciable central nervous system (CNS) activity was produced by ketorolac. It did not possess anticonvulsant activity in mice in the maximal electroshock test nor did it inhibit pentylentetrazol-induced seizures in mice or rats.

In mice, hexobarbital-induced sleep time was unaltered by ketorolac suggesting that the compound was not a CNS depressant.

The gross behavior and sleep patterns of cats dosed at up to 10 mg/kg, i.v., were unchanged.
Cardiovascular Effects:
Sequential administration of 1, 3 and 10 mg/kg, i.v. of ketorolac to anesthetized cats, produced minimal cardiovascular or autonomic responses.

In anesthetized dogs, doses of 1 to 30 mg/kg, i.v. produced inconsistent and variable changes in the cardiac contractile force, heart rate and blood pressure. The cardiovascular responses to adrenaline, nor-adrenaline, tyramine, phenylephrine and bilateral carotid artery occlusion were inhibited by ketorolac, suggesting that the compound may possess mild alpha-adrenoceptor blocking activity.

Bronchial Effects:
Ketorolac, when administered intravenously to guinea pigs in doses of 0.01 - 10 mg/kg failed to block histamine- or methacholine-induced bronchoconstriction. In the rat, the compound blocked methacholine-induced airway constriction (ED50 = 0.5 mg/kg).

Gastric Effects:
Doses of ketorolac at 0.1 and 1.0 mg/kg p.o. in rats did not alter significantly either the gastric juice volume or the total mEq of hydrogen ions secreted in response to histamine stimulation. Moreover, in common with other NSAIDs, both the acid and the tromethamine salt of ketorolac had a similar propensity to cause gastrointestinal erosions in rats independent of the route of administration.

Pharmacokinetics
A series of studies were carried out in mice, rats, rabbits, monkeys and humans to characterize the pharmacokinetic profile of the free acid of ketorolac and ketorolac tromethamine. The salt form of the compound was later selected for development due to its more rapid and complete absorption.

Ketorolac tromethamine was rapidly (Tmax ranged from 0.25 - 1.5hr) and completely absorbed after oral and i.m. doses in animals (>87%) and humans (>99%). 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. The plasma half life of ketorolac ranged from 2.1 hours in rabbits to 6.6 hours in rhesus monkeys and 7.7 hours in mice. In humans, the plasma half life averaged 6.0 hours. The volume of distribution of ketorolac was estimated following intravenous dosing and ranged from 0.09 L/kg in mice to 0.38 L/kg in rats; in humans it averaged 0.15 L/kg. Total plasma clearance ranged from 0.44 mL/min/kg in mice to 2.44 mL/min/kg in rats and averaged 0.35 mL/min/kg in humans.
Ketorolac was highly protein bound in human (99.2%), monkey (98.3%) and rabbit (98.2%) plasma; moderately bound in rat plasma (92.1%); and poorly bound in mouse plasma (72.0%). Binding was concentration independent in all species studied.

The tissue distribution of ketorolac-associated radioactivity was studied in male mice. The highest levels were found in the kidney which was the only organ which exceeded plasma levels at all time points (by about 50%). The lowest levels were present in the brain. However, all tissues eliminated ketorolac-associated radioactivity rapidly with a tissue half life of < 3.6 hours.

Distribution studies in pregnant rabbits and rats showed that ketorolac-associated radioactivity distributed into the fetus in low but measurable levels - less than 15% in rabbits and 6% in rats based upon fetal to maternal plasma or blood concentration ratios. Ketorolac-associated radioactivity was also passed into the milk of lactating animals. In rats, radioactivity concentrations in milk exceeded plasma concentrations at all time points by as much as four fold. However, in rabbits, milk concentrations were only about 12% of plasma concentrations.

**Metabolism:**

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

A moderate first pass metabolism (about 20%) was observed in humans, while rabbits exhibited more extensive first pass metabolism (about 50%) following oral doses.

The metabolism and excretion patterns of ketorolac and its metabolites were similar following p.o., i.v. and i.m. dosing in the species studied. Ketorolac accounted for most of the radioactivity circulating in the plasma ranging from 79% in rabbits to 99% in mice and averaged 96% in humans. Conjugates of ketorolac were not detected in plasma in appreciable amounts in any species. However, the p-hydroxy metabolite (which is essentially inactive when compared to ketorolac) was detected in the plasma of rats, rabbits and humans. Ketorolac and its metabolites were excreted predominantly in the urine of all species, ranging from 69% in rats to essentially 100% in the cynomolgus monkey and averaged 92% in humans. The most comparable species with respect to man metabolically was the mouse.
## TOXICOLOGY

### Acute Toxicity Studies

<table>
<thead>
<tr>
<th>Animal</th>
<th>Strain</th>
<th>Sex</th>
<th>Route</th>
<th>LD 50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>HLA-SW/ICR</td>
<td>F</td>
<td>Oral</td>
<td>approx. 400</td>
</tr>
<tr>
<td>Mouse</td>
<td>HLA-SW/ICR</td>
<td>M/F</td>
<td>Oral+</td>
<td>529 (281 - 1540)*</td>
</tr>
<tr>
<td>Rat</td>
<td>COX-SD</td>
<td>F</td>
<td>Oral</td>
<td>112 (68 - 191)*</td>
</tr>
<tr>
<td>Rat</td>
<td>COX-SD</td>
<td>M/F</td>
<td>Oral+</td>
<td>100 - 400</td>
</tr>
<tr>
<td>Mouse</td>
<td>HLA-SW/ICR</td>
<td>F</td>
<td>i.p.</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Mouse</td>
<td>HLA-SW/ICR</td>
<td>M/F</td>
<td>i.p.+</td>
<td>473 (315 - 771)*</td>
</tr>
<tr>
<td>Rat</td>
<td>COX-SD</td>
<td>F</td>
<td>i.p.</td>
<td>158 (101 - 248)*</td>
</tr>
<tr>
<td>Rat</td>
<td>COX-SD</td>
<td>M/F</td>
<td>i.p.+</td>
<td>100 - 400</td>
</tr>
</tbody>
</table>

Note:  
* 95% confidence interval  
+ studies with ketorolac tromethamine; all others with ketorolac free acid. All doses were administered in solution form.

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

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

### Sensitization:

The sensitization potential of a 0.1% solution of ketorolac tromethamine was evaluated in male guinea pigs. Ketorolac tromethamine did not cause sensitization when tested in the guinea pig model.
Vein Irritation:
An intravenous formulation containing ketorolac tromethamine at a concentration of 10 mg/mL was injected into the marginal ear vein of the left ear of each of 6 rabbits (New Zealand albino). The right ear served as a sham control. No evidence of vein irritation was seen following gross or microscopic pathological examinations.

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

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.

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

Daily oral administration of ketorolac to monkeys at doses of 0.0 (vehicle control), 0.5, 2, 8 or 32 mg/kg/day for 4 weeks resulted in clinical signs of toxicity, and hematologic and pathologic effects at all dose levels. Clinically, a few isolated instances of dark colored urine, vomiting and dark colored feces (fecal blood) were seen in all dose groups but not in controls. There was a slight decrease in hemoglobin and hematocrit levels mainly in the high dose group animals. Other parameters, such as body weight, ophthalmoscopy, clinical chemistry and urinalysis, were all comparable to control values. Gastric erosions were observed in some animals at all dose levels, while gastric ulceration and hemorrhage were seen in some animals receiving 8 or 32 mg/kg/day. Chronic colitis was seen in 3 out of 4 monkeys treated with the highest dose.
**Intravenous:**
Intravenous administration of ketorolac tromethamine to rabbits and monkeys at doses of 0 (vehicle), 0.5, 1.25 or 2.5 mg/kg/day for 2 weeks was well tolerated with no clinically significant treatment related effects.

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

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

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

There were no clinical signs of drug related systemic toxicity. However, the incidence and severity of lacerations and ulcers of the extremities (limbs and tail) were increased in the drug treated groups compared to the controls. These lesions were probably the result of bite wounds and the analgesic effect of the drug may have reduced the normal avoidance behavior in response to painful stimuli.

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

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

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

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

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

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

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

Two groups each with 5 male and 5 female cynomolgus monkeys were administered once daily 0.75 or 2.62 mg/kg of ketorolac tromethamine for 12 months. Two additional groups each with 8 males and 8 females received vehicle only or 9 mg/kg of ketorolac tromethamine for 12 months. All groups received 1.5 mL/kg/day of formulation administered into the stomach by nasal catheter. Three males and three female monkeys from the high dose and vehicle treated groups had a recovery period from dosing of months and then were given clinical laboratory analysis and a complete necropsy at the end of the 12 month dosing period.

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

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

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

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

**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.

**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.

**Fertility and Reproduction**

**Female Rat:**

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

No treatment-related effects were seen on the reproductive status at gestation day 13. Some treated females died during the study and the deaths were attributed to gastroenteropathy, nephropathy, or dystocia.
The length of gestation was significantly increased in the high-dose (P1 females) group (median 25 days) when compared to the controls (median 22 days). A slight increase in the length of gestation (median 22.5 days) was noted in the mid-dose group when compared to the controls. Decreased live litter sizes and survival indices were noted in the high-dose group when compared to controls. No pups from the high dose group survived to day 4 of postnatal life. Decreased survival indices (up to day 7) were noted in the mid-dose group when compared to controls. The maternal care and lactation data were comparable among the control, low and mid-dose groups. The clinical condition and body weights of surviving F1 pups were comparable among all groups. The postnatal behavioral and developmental evaluation of F1 pups indicated no treatment-related effects. The reproductive performance of the F1 pups and the neonatal survival of their offspring (F2 pups) were comparable among the groups.

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

**Male Rat:**

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

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

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

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

**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 embryolethality were observed. External and skeletal or visceral examinations of fetuses did not reveal any teratogenic changes attributable to the test compound.
Administration of ketorolac tromethamine, to female rabbits during organogenesis (day 6 through day 18 of gestation) by gavage, once daily at doses of 0.1, 0.6 or 3.6 mg/kg/day was not teratogenic.

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

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


