

PRODUCT MONOGRAPH

KETOROLAC **Ketorolac Tromethamine Tablets** **10 mg**

NSAID Analgesic Agent

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PRODUCT MONOGRAPH

KETOROLAC

Ketorolac Tromethamine Tablets

Apotex Standard

10 mg

PHARMACOLOGIC/THERAPEUTIC CLASSIFICATION

NSAID Analgesic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

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 cyclo-oxygenase enzyme system. At analgesic doses, it has minimal anti-inflammatory and antipyretic activity.

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, and the pharmacokinetics are linear following single and multiple dosing. Steady state plasma levels are attained after one day of q.i.d. dosing.

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

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

The Influence of Age, Liver and Kidney Function on the Clearance and Terminal Half-Life of Oral¹ Ketorolac Tromethamine		
Types of Subjects	Total Clearance (in L/h/kg)²	Terminal Half-Life (in hours)
	Mean (range)	Mean (range)
Normal Subjects (n=77)	0.025 (0.013-0.050)	5.3 (2.4-9.0)
Healthy Elderly Subjects (n=12) (mean age=72, range=65-78)	0.024 (0.018-0.034)	6.1 (4.3-7.6)
Patients with Hepatic Dysfunction (n=7)	0.033 (0.019-0.051)	4.5 (1.6-7.6)
Patients with Renal Impairment (n=9) (serum creatinine 1.9-5.0 mg/dL)	0.016 (0.007-0.052)	10.8 (3.4-18.9)

¹Estimated from 10 mg single oral doses of ketorolac tromethamine.

²Litres/hour/kilogram.

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.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of ketorolac following administration of a single 30 mg dose (three 10 mg tablets) of KETOROLAC and Toradol® were measured and compared. The results from measured data are summarized as follows:

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Means (%)**
	KETOROLAC	Toradol®†	
AUC _T (ng·hr/mL)	8913 9027 (16)	8854 9020 (20)	100.7
AUC _I (ng·hr/mL)	9797 9957 (19)	9812 10043 (22)	99.9
C _{max} (ng/mL)	2720 2757 (17)	2611 2685 (23)	104.1
T _{max} * (hr)	0.71 (77)	0.74 (64)	--
t _{1/2} * (hr)	4.62 (16)	4.83 (20)	--

* The T_{max} and t_{1/2} parameters are expressed as the arithmetic means.

**Based on the least square estimates.

†Toradol® (Hoffmann-La Roche Ltd.) was purchased at a Canadian retail pharmacy.

INDICATIONS AND CLINICAL USE

KETOROLAC (ketorolac tromethamine) is indicated for the short-term management (not to exceed 5 days for post-surgical patients or 7 days for patients with musculoskeletal pain) of moderate to moderately severe acute pain, including post-surgical pain (such as general, orthopaedic and dental surgery), acute musculoskeletal trauma pain and post-partum uterine cramping pain (see WARNINGS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

The following are contraindications to the use of KETOROLAC (Ketorolac Tromethamine):

- 1) Patients with active peptic ulcer disease, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system. Severe and fatal reactions have occurred in such individuals.
- 2) Known or suspected hypersensitivity to the drug or other NSAIDs. The potential for cross-reactivity between different NSAIDs must be kept in mind.

KETOROLAC should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, 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 effects.

- 3) Significant hepatic impairment or active liver disease.
- 4) Patients with moderate to severe renal impairment (serum creatinine $>442 \mu\text{mol/L}$) or in patients at risk for renal failure due to volume depletion or dehydration. Individual with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.
- 5) The use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.
- 6) Immediately before any major surgery, and is contraindicated intraoperatively when haemostasis is critical because of the increased risk of bleeding. KETOROLAC is also contraindicated in patients with coagulation disorders, postoperative patients with high haemorrhagic risk or incomplete haemostasis, and in patients with suspected or confirmed cerebrovascular bleeding.
- 7) In labour and delivery because, through its prostaglandin synthesis inhibitory effect, ketorolac tromethamine may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine haemorrhage.
- 8) The concomitant use of KETOROLAC and probenecid.
- 9) The combination of KETOROLAC and oxpentifylline (see PRECAUTIONS, Drug Interactions).

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 CLINICAL USE and DOSAGE AND ADMINISTRATION).

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

Gastrointestinal System (GI)

Gastrointestinal mucosal injury may occur. Serious gastrointestinal toxicity, such as bleeding, peptic ulceration, perforation and gastrointestinal bleeding, **sometimes severe and occasionally fatal** can occur at any time, with or without warning symptoms, during therapy with NSAIDs including ketorolac tromethamine.

Minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with NSAIDs, even in the absence of previous gastrointestinal tract symptoms. In patients observed in clinical trials of such agents, symptomatic upper gastrointestinal ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months and in about 2 to 4% of patients treated for 1 year. The risk continues beyond 1 year and possibly increases.

The incidence of these complications increases with increasing dose.

The long-term use of ketorolac is not recommended.

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

Physicians should inform patients about the signs and/or symptoms of serious gastrointestinal toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

If ulceration is suspected or confirmed, or if gastrointestinal bleeding occurs, ketorolac tromethamine should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies to date have identified any group of patients **not** at risk of developing ulceration and bleeding. A prior history of serious gastrointestinal events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anticoagulant use have been associated with increased risk.

Studies to date show that all NSAIDs can cause gastrointestinal tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

Use in the Elderly

Patients older than 65 years and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to the effects of ulceration and bleeding. Older patients are also at risk of lower esophageal ulceration and bleeding. Postmarketing experience with ketorolac 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. Because ketorolac is cleared somewhat more slowly by the elderly (see PHARMACOLOGY, Pharmacokinetics) extra caution and the lowest effective dose should be used (see DOSAGE AND ADMINISTRATION).

Hypersensitivity Reactions

The possibility of severe or fatal hypersensitivity reactions (including, but not limited to, anaphylaxis, bronchospasm, flushing, rash, hypotension, laryngeal edema, angioedema) should be considered, even for patients with no known history of previous exposure or hypersensitivity to ketorolac tromethamine, ASA or other NSAIDs. As with other NSAIDs, patients should be questioned for history of allergy to NSAIDs or ASA, angioedema, bronchospastic activity 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.

Cross-Sensitivity

Patients sensitive to any one of the NSAIDs may be sensitive to any of the other NSAIDs also.

Aseptic Meningitis

In occasional cases, 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 physician must be vigilant to the development of this complication.

Use in Pregnancy, Labor and Lactation

The administration of ketorolac tromethamine is not recommended during pregnancy. Ketorolac is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage (see CONTRAINDICATIONS).

The administration of ketorolac tromethamine is not recommended during lactation. Ketorolac should be used by nursing mothers only if the potential benefit justifies the potential risk to the fetus. After 1 day at 10 mg q.i.d. oral dosing, ketorolac has been detected in the milk of lactating women at a maximum concentration of 7.9 ng/mL.

There was no evidence of teratogenicity in rats or rabbits studied at maternally-toxic doses of ketorolac. Prolongation of the gestation period and/or delayed parturition were seen in the rat. Ketorolac crosses the placenta to the extent of approximately 10%.

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.

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.

Discontinuation of ketorolac tromethamine or other nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

Haemorrhage

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 haemostasis, careful observation is advised.

Use of ketorolac tromethamine in patients who are receiving therapy that affects haemostasis should be undertaken with caution, including close monitoring. The concurrent use of ketorolac tromethamine and prophylactic, low dose heparin (2500 - 5000 units q.12.h.), warfarin and dextrans may also be associated with an increased risk of bleeding (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS

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

Gastrointestinal System

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

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

Genitourinary Tract

Some NSAIDs are known to cause 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, treatment with ketorolac tromethamine **must be stopped immediately** to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic Function

Caution should be observed if ketorolac tromethamine is to be used in patients with impaired hepatic function, or a history of liver disease. As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Meaningful elevations (greater than 3 times normal) of ALT and AST, occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions including jaundice and cases of fatal hepatitis 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, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ketorolac should be discontinued. Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac clearance. Studies in patients with active hepatitis or cholestasis have not been performed.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance

Fluid retention, edema, hypertension, 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.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β -adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics.

Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully

observed when ketorolac is administered.

Ketorolac 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 is normalized within 24 to 48 hours after the drug is discontinued.

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.

Infection

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

Ophthalmology

Blurred and/or diminished vision has been reported with the use of ketorolac tromethamine and other NSAIDs. If such symptoms develop, this drug should be discontinued and an ophthalmologic examination performed.

Central Nervous System

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of ketorolac tromethamine. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Concomitant Medications

In patients currently receiving ASA or other NSAIDs, the risk of serious NSAID-related adverse events may be increased. When ketorolac tromethamine is administered concurrently with oxpentifylline, there is an increased tendency to bleeding (see CONTRAINDICATIONS).

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, tolbutamide, ibuprofen, naproxen and piroxicam did not alter ketorolac tromethamine protein binding.

Anticoagulant Therapy: Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of gastrointestinal adverse events such as ulceration and bleeding. Because prostaglandins play an important role in haemostasis, and NSAIDs affect platelet function, concurrent therapy of ketorolac with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary (see PRECAUTIONS).

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

The *in vitro* binding of warfarin to plasma proteins is only slightly reduced by ketorolac (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 or Other NSAIDs: The use of ketorolac tromethamine in addition to any other NSAID, including those over the counter ones (such as ASA and ibuprofen) is contraindicated due to the possibility of additive side effects. *In vitro* studies indicated that, at therapeutic concentrations of salicylates (300 mcg/mL), the binding of ketorolac tromethamine was reduced from approximately 99.2% to 97.5% representing a potential two-fold increase in unbound ketorolac tromethamine plasma levels.

Glucocorticoids: Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of gastrointestinal side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

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 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). The concomitant use of ketorolac tromethamine and probenecid is, therefore, contraindicated.

Furosemide: 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.

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. Cases of increased lithium plasma concentrations during ketorolac tromethamine therapy have been reported.

Methotrexate: The concomitant administration of methotrexate and some NSAIDs has been reported to reduce the clearance of methotrexate, thus enhancing its toxicity.

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

ADVERSE REACTIONS

The most common adverse reaction encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

KETOROLAC TROMETHAMINE TABLETS

Short-Term Patient Studies

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

Incidence Between 4 and 9%:

Nervous system:	somnolence, insomnia
Digestive system:	nausea

Incidence Between 2 and 3%:

Nervous system:	nervousness, headache, dizziness
Digestive system:	diarrhea, dyspepsia, gastrointestinal pain, constipation
Body as a whole:	fever

Incidence 1% or Less:

Nervous system: abnormal dreams, anxiety, dry mouth, hyperkinesia, paresthesia, increased sweating, euphoria, hallucinations

Digestive system: anorexia, flatulence, vomiting, stomatitis, gastritis, gastrointestinal disorder, sore throat

Body as a whole: asthenia, pain, back pain

Cardiovascular system: vasodilatation, palpitation, migraine, hypertension

Respiratory system: cough increased, rhinitis, dry nose

Musculoskeletal system: myalgia, arthralgia

Skin and appendages: rash, urticaria

Special senses: blurred vision, ear pain

Urogenital system: dysuria

Long-Term Patient Study

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

Incidence Between 10 and 12%:

Digestive system: dyspepsia, gastrointestinal pain

Incidence Between 4 and 9%:

Digestive system: nausea, constipation

Nervous system: headache

Incidence Between 2 and 3%:

Digestive system: diarrhea, flatulence, gastrointestinal fullness, peptic ulcers

Nervous system: dizziness, somnolence

Metabolic/nutritional disorder: edema

Incidence 1% or Less:

Digestive system: eructation, stomatitis, vomiting, anorexia, duodenal ulcer, gastritis, gastrointestinal haemorrhage, increased appetite, melena, mouth ulceration, rectal bleeding, sore mouth

Nervous system: abnormal dreams, anxiety, depression, dry mouth, insomnia, nervousness, paresthesia

Special senses: tinnitus, taste perversion, abnormal vision, blurred vision, deafness, lacrimation disorder

Metabolic/nutritional disorder: weight gain, alkaline phosphatase increase, BUN increased, excessive thirst, generalized edema, hyperuricemia

Skin and appendages: pruritus, rash, burning sensation skin

Body as a whole: asthenia, pain, back pain, face edema, hernia

Musculoskeletal system: arthralgia, myalgia, joint disorder

Cardiovascular system: chest pain, chest pain substernal, migraine

Respiratory system: dyspnea, asthma, epistaxis

Urogenital system: haematuria, increased urinary frequency, oliguria, polyuria

Haemic and lymphatic: anemia, purpura

POSTMARKETING EXPERIENCE

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

Renal Events

Acute renal failure, flank pain with or without haematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, haemolytic uremic syndrome, urinary retention.

Hypersensitivity Reactions

Bronchospasm, laryngeal edema, asthma, hypotension, flushing, rash, anaphylaxis, angioedema and anaphylactoid reactions. Such reactions have occurred in patients with no prior history of hypersensitivity.

Gastrointestinal Events

Gastrointestinal haemorrhage, peptic ulceration, gastrointestinal perforation, pancreatitis, melena, esophagitis, haematemesis.

Haematologic Events

Postoperative wound haemorrhage, rarely requiring blood transfusion (see PRECAUTIONS), thrombocytopenia, epistaxis, leukopenia, haematomata, increased bleeding time.

Central Nervous System

Convulsions, abnormal dreams, hallucinations, hyperkinesia, hearing loss, aseptic meningitis, extrapyramidal symptoms, psychotic reactions.

Hepatic Events

Hepatitis, liver failure, cholestatic jaundice.

Cardiovascular

Pulmonary edema, hypotension, flushing, bradycardia.

Dermatology

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

Body as Whole

Infection.

Urogenital

Interstitial nephritis, nephrotic syndrome, raised serum urea and creatinine.

SYMPTOMS AND TREATMENT OF 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 overdose. Single doses of ketorolac have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing. 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.

The usual oral dose of KETOROLAC (ketorolac tromethamine) is 10 mg every 4 to 6 hours for pain as required. Doses exceeding 40 mg per day are not recommended. The maximum

duration of treatment with the oral formulation is 5 days for post-surgical patients and 7 days for patients with musculoskeletal pain.

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

The lowest effective dose is recommended.

Impaired Renal Function

Ketorolac and its metabolites are eliminated by the kidneys, which in patients with reduced creatinine clearance, will result in diminished plasma clearance of the drug. KETOROLAC is contraindicated in patients with moderate to severe renal impairment (serum creatinine $>442 \mu\text{mol/L}$) (see CONTRAINDICATIONS). KETOROLAC should be used with caution in patients with lesser renal impairment (serum creatinine 170 to $442 \mu\text{mol/L}$). Such patients should receive a reduced dose of ketorolac, and their renal status should be closely monitored. It is recommended that the daily dose be reduced by half; a total daily dose of 60 mg should not be exceeded. Dialysis does not significantly clear ketorolac from blood stream.

Conversion from Parenteral To Oral Therapy

KETOROLAC Tablets may be used either as monotherapy or as follow-on therapy to parenteral ketorolac.

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

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

KETOROLAC (ketorolac tromethamine) is a Schedule F drug.

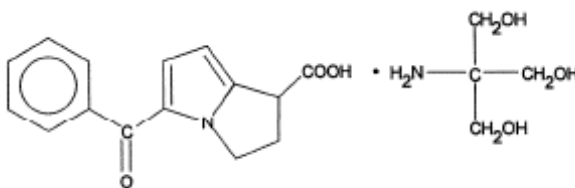
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Ketorolac tromethamine

ne: (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid,
2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Structural Formula:



Molecular Formula: C₁₉H₂₄N₂O₆

Molecular Weight: 376.41

Description: Ketorolac tromethamine (pKa = 3.46) is an off-white to white crystalline powder that melts at about 162°C with decomposition. 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 - 6.7.

COMPOSITION

KETOROLAC (Ketorolac Tromethamine) Tablets

In addition to ketorolac tromethamine, each 10 mg film coated tablet contains the non-medicinal ingredients magnesium stearate, croscarmellose sodium, lactose, microcrystalline cellulose, hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol.

STABILITY AND STORAGE RECOMMENDATIONS

KETOROLAC (Ketorolac Tromethamine) Tablets

Store at room temperature 15-30°C (59-86°F). Protect from light.

AVAILABILITY OF DOSAGE FORMS

KETOROLAC (Ketorolac Tromethamine) Tablets

Each round, white, biconvex, film coated tablet engraved "KE" over "10" on one side contains 10 mg of ketorolac tromethamine. Available in bottles of 100 and 500 tablets.

INFORMATION FOR THE PATIENT

KETOROLAC TABLETS

HOW TO MAKE KETOROLAC WORK BEST FOR YOU

Your doctor has decided that KETOROLAC (ketorolac tromethamine) is the best treatment for you. As you take your KETOROLAC tablets, remember that your chances of controlling your symptoms are greater if you cooperate fully with your doctor and try to become well informed about your condition.

This leaflet is not as thorough as the official Product Monograph on KETOROLAC (which your doctor or pharmacist has available) and is meant to supplement what your doctor has told you. Your doctor knows and understands your personal condition. Be sure to follow your doctor's instructions carefully and read any materials he or she gives you. **If you have any questions after reading this information leaflet, be sure to ask your doctor.**

WHAT IS KETOROLAC?

- KETOROLAC tablets contain ketorolac tromethamine, a member of the class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs).
- KETOROLAC tablets are used for the short-term relief of pain including pain that occurs following surgery (such as general, orthopaedic and dental surgery), and post-partum uterine cramping pain. It is also used for pain relief following injuries.

HOW DOES KETOROLAC WORK?

KETOROLAC helps to relieve pain by reducing the production of certain pain-causing substances called prostaglandins. Clinical studies indicate that when prostaglandin levels are reduced, the intensity of pain is reduced as well.

HOW SHOULD KETOROLAC BE TAKEN?

You should take KETOROLAC tablets only as directed by your doctor. Do not take more of them, do not take them more often and do not take them for a longer period of time than your doctor or dentist ordered. Taking too much of KETOROLAC tablets may increase the chance of unwanted effects, especially if you are an elderly patient.

Stomach upset is one of the common problems with NSAIDs: To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e., do not lie down) for about 15 to 30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

IMPORTANT! Your doctor may give you different instructions better suited to your specific needs. If you need more information about how to take KETOROLAC properly, double-check with your doctor or pharmacist.

HOW LONG DOES IT TAKE BEFORE KETOROLAC BEGINS TO WORK?

Some people are able to feel improvement in their symptoms right away; for others, improvement may take up to one day. By the end of one day, if KETOROLAC does not seem to be helping you, tell your doctor. You may need a different dosage or your doctor may want to prescribe another treatment program for you.

ALWAYS REMEMBER: The risks of taking this medication must be weighed against the benefits it will have.

Before taking KETOROLAC tell your doctor and pharmacist if you:

- or a family member are allergic to or have had a reaction to ketorolac or other anti-inflammatory drugs (such as acetylsalicylic acid [ASA], diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, piroxicam,

tiaprofenic acid, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse). Please consult your doctor or pharmacist if you are unsure what your product contains. A partial list of brand name products which contain ASA, NSAIDs or ibuprofen is included at the end of this leaflet.

- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);
- have a history of stomach upset, ulcers, liver or kidney diseases;
- have blood or urine abnormalities;
- have high blood pressure;
- have diabetes;
- are on any special diet, such as a low-sodium or low-sugar diet;
- are pregnant or intend to become pregnant while taking this medication;
- are breast-feeding or intend to breast-feed while taking this medication;
- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporine, lithium, phenytoin;
- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

While taking KETOROLAC:

- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;
- some NSAIDs may cause drowsiness or fatigue in some people taking them. Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your doctor if you are not getting any relief of your pain or if any problems develop;
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;
- check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;
- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the

skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your doctor;

- check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication.

DOES KETOROLAC HAVE ANY SIDE-EFFECTS?

Along with its beneficial effects, KETOROLAC like other NSAID drugs, may cause some undesirable reactions especially when used in large doses. It is important to note that long-term use of KETOROLAC is not recommended.

Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects.

Although not all of these side effects are common, when they do occur they may require medical attention.

Check with your doctor immediately if any of the following are noted:

- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing, or tightness in the chest;
- skin rash, hives or swelling, itching;
- vomiting or persistent indigestion, nausea, stomach pain or diarrhea;
- yellow discoloration of the skin or eyes;
- any change in the amount of or colour of your urine (dark red or brown);
- any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- malaise, fatigue, loss of appetite;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;
- hearing problems.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

DOSING

The usual oral dose of KETOROLAC in adults is 10 mg (1 tablet) every 4 to 6 hours for pain as required. Doses exceeding 40 mg per day (4 tablets) are not recommended.

KETOROLAC may be taken after a meal or with food or milk if desired. However, the presence of food in the stomach may delay the onset of pain relief. If stomach upset occurs (indigestion, nausea, vomiting, stomach pain or diarrhea) contact your doctor.

KETOROLAC tablets are recommended for short-term use only (not to exceed 5 days following surgery or 7 days for patients with pain from muscular strains, sprains and injuries).

For patients whose weight is under 50 kg or are over the age of 65 years or with less severe pain to start with, the lowest effective dose is recommended.

What to do if you miss a dose: If you forget to take a dose of KETOROLAC take it as soon as possible, then just carry on with the regular times you take your medication. If you remember your missed dose close to the time for your next dose, do not take the missed dose.

Storage: KETOROLAC should be stored at room temperature 15-30°C (59-86°F). Protect from light.

KETOROLAC is not recommended for use in patients under 16 years of age since safety and effectiveness have not been established.

Do not keep outdated medicine or medicine no longer needed.

Keep out of the reach of children.

This medication has been prescribed for your medical problem. Do not give it to anyone else.

If you require more information on this drug, consult your doctor or pharmacist.

ASA-Containing OTC Brands	NSAID-Containing Brands	Ibuprofen-Containing Brands
Anacin, Bufferin, Aspirin, Alka-Seltzer, C2, Entrophen, 222, Midol, Robaxisal, Coricidin D, Dristan Tablets	Voltaren, Arthrotec, Dolobid, Nalfon, Froben, Ansaid, Indocid, Orudis, Ponstan, Naprosyn, Feldene, Clinoril, Mobiflex, Surgam, Tolectin, Idarac, Motrin, Anaprox, Relafen, Toradol	Advil, Actiprofen, Nuprin, Medipren, Motrin IB.

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 pentylenetetrazol-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, noradrenaline, 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 ($ED_{50} = 0.5$ 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 (T_{max} ranged from 0.25 - 1.5 hr) 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

Animal	Strain	Sex	Route	LD₅₀ (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

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 coloured 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.

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.

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 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.

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