1 NAME OF THE MEDICINAL PRODUCT

Dolac Tablets (Ketorolac Tromethamine Tablets USP, 10mg)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains
Ketorolac Tromethamine USP 10mg.
Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carefully consider the potential benefits and risks of ketorolac tromethamine and other treatment options before deciding to use ketorolac tromethamine. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Acute Pain in Adult Patients

Ketorolac tromethamine tablets are indicated for the short-term (≤ 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with ketorolac tromethamine-IV or IM and ketorolac tromethamine tablets are to be used only as continuation treatment, if necessary.

The total combined duration of use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine tablet therapy is not to exceed 5 days.

4.2 Posology and method of administration

Carefully consider the potential benefits and risks of ketorolac tromethamine and other treatment options before deciding to use ketorolac tromethamine. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. In adults, the combined duration of use of IV or IM dosing of ketorolac tromethamine and ketorolac tromethamine tablets is not to exceed 5 days. In adults, the use of ketorolac tromethamine tablets is only indicated as continuation therapy to IV or IM dosing of ketorolac tromethamine.

Transition from IV or IM dosing of ketorolac tromethamine (single- or multiple-dose) to multiple-dose ketorolac tromethamine tablets:

Pediatric Patients: There are no data available to support the use of ketorolac tromethamine tablets in pediatric patients.

Patients age 17 to 64: 20 mg PO once followed by 10 mg q4 to 6 hours prn not >40 mg/day.

Patients age >65, renally impaired, and/or weight < 50 kg (110 lbs): 10 mg PO once followed by 10 mg q4 to 6 hours prn not >40 mg/day 40 mg/day.

Note:

- Oral formulation should not be given as an initial dose
- Use minimum effective dose for the individual patient
- Do not shorten dosing interval of 4 to 6 hours

Total duration of treatment in adult patients: The combined duration of use of IV or IM dosing of ketorolac tromethamine and ketorolac tromethamine tablets is not to exceed 5 days.

The following table summarizes ketorolac tromethamine tablets dosing instructions in terms of age group:

Table 2: Summary of Dosing Instructions

Patient Population	**Ketorolac Tromethamine Tablets (following IV or IM dosing of ketorolac tromethamine)**
Age < 17 years	Oral not approved
Adult Age 17 to 64 years	20 mg once, then 10 mg q4 to 6 hours PRN not > 40 mg/day
Adult Age > 65 years, renally impaired and/or weight <50 kg	10 mg once, then 10 mg q4 to 6 hours PRN not > 40 mg/day

4.3 Contraindications

- Ketorolac tromethamine is contraindicated in patients with previously demonstrated hypersensitivity to ketorolac tromethamine.
- Ketorolac tromethamine is contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.
- Ketorolac tromethamine should not be given to patients who have experienced asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDS. Severe, rarely fatal, anaphylactic-like reactions to NSAIDS have been reported in such patients.
- Ketorolac tromethamine is contraindicated as prophylactic analgesic before any major surgery.
- Ketorolac tromethamine is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Ketorolac tromethamine is contraindicated in patients with advanced renal impairment or in patients at risk for renal failure due to volume depletion.
- Ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fatal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage.
- The use of ketorolac tromethamine is contraindicated in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.
- Ketorolac tromethamine inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, haemorrhagic diathesis, incomplete homeostasis and those at high risk of bleeding.
- Ketorolac tromethamine is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events.
- The concomitant use of ketorolac tromethamine and probenecid is contraindicated.
- The concomitant use of ketorolac tromethamine and pentoxifylline is contraindicated.

4.4 Special warnings and precautions for use

The total combined duration of use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days in adults. Ketorolac tromethamine tablets are not indicated for use in paediatric patients. The most serious risks associated with ketorolac tromethamine are:

Gastrointestinal Effects – Risk of Ulceration, Bleeding and Perforation

Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or GI bleeding. Ketorolac tromethamine can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration and perforation, of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. Do not use ketorolac tromethamine for more than 5 days. However, even short-term therapy is not without risk. In addition to past history of ulcer disease, other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids, or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.
Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of ketorolac tromethamine until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

Haemorrhage
Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and therapy that affects hemostasis, including prophylactic low-dose heparin (2500 to 5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks and use such concomitant therapy in these patients only extremely cautiously. Patients receiving therapy that affects hemostasis should be monitored closely.

In post-marketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the perioperative use of IV or IM dosing of ketorolac tromethamine. Therefore, perioperative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug. Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, interstitial nephritis and nephrotic syndrome.

Impaired Renal Function
Ketorolac tromethamine is contraindicated in patients with serum creatinine concentrations indicating advanced renal impairment. Ketorolac tromethamine should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Because patients with underlying renal insufficiency are at increased risk of developing acute renal decompensation or failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without a known previous exposure or hypersensitivity to ketorolac tromethamine. Ketorolac tromethamine should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Cardiovascular Effects
Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ketorolac tromethamine, increases the risk of serious gastrointestinal (GI) events.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG.
Post-MI Patients

Observational studies conducted have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next 4 years of follow-up.

Avoid the use of ketorolac tromethamine in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ketorolac tromethamine is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Hypertension
NSAIDs, including ketorolac tromethamine, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ketorolac tromethamine, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ketorolac tromethamine may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)].
Avoid the use of ketorolac tromethamine in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ketorolac tromethamine is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Skin Reactions
NSAIDS, including ketorolac tromethamine, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity**.**

General
Ketorolac tromethamine cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
The pharmacological activity of ketorolac tromethamine in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effect
Ketorolac tromethamine should be used with caution in patients with impaired hepatic function or a history of liver disease. Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including ketorolac tromethamine. These laboratory abnormalities may progress, may remain unchanged or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketorolac tromethamine. 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.

Hematologic Effect
Anaemia is sometimes seen in patients receiving NSAIDs, including ketorolac tromethamine. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis.

Patients on long-term treatment with NSAIDs, including ketorolac tromethamine, should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ketorolac tromethamine who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ketorolac tromethamine should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients
Ketorolac tromethamine is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing ketorolac tromethamine, should inform their patients or their guardians of the potential risks of ketorolac tromethamine treatment, instruct patients to seek medical advice if they develop treatment-related adverse events, and advise patients not to give ketorolac tromethamine tablets to other family members and to discard any unused drug.

Remember that the total combined duration of use of ketorolac tromethamine tablet and ketorolac tromethamine IV or IM dosing is not to exceed 5 days in adults. Ketorolac tromethamine tablets are not indicated for use in paediatric patients.

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.

- Cardiovascular Thrombotic Events: Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately.
- Ketorolac tromethamine, like other NSAIDs, can cause GI discomfort and rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena and hematemesis. Patients should be apprised of the importance of this follow-up.
- Ketorolac tromethamine, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
- Heart Failure and Edema: Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur.
- Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
- Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help.
- In late pregnancy, as with other NSAIDs, ketorolac tromethamine should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, ketorolac tromethamine should be discontinued.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Paediatric Use
Ketorolac tromethamine 10mg tablets are not indicated for use in paediatric patients. The safety and effectiveness of ketorolac tromethamine tablets in paediatric patients below the age of 17 have not been established.

Geriatric Use (≥ 65 years of age)
Because ketorolac tromethamine may be cleared more slowly by the elderly who are also more sensitive to the dose related adverse effects of NSAIDs, extreme caution, reduced dosages and careful clinical monitoring must be used when treating the elderly with ketorolac tromethamine.

Effects on Fertility
The use of ketorolac tromethamine, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of ketorolac tromethamine should be considered.

4.5 Interaction with other medicinal products and other forms of interaction
Ketorolac is highly bound to human plasma protein (mean 99.2%). There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Warfarin, Digoxin, Salicylate and Heparin
The *in vitro* binding of *warfarin* to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs. 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter *digoxin* protein binding. *In vitro* studies indicate that, at therapeutic concentrations of *salicylate* (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential 2-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of *digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin* and *tolbutamide* did not alter ketorolac tromethamine protein binding.

In a study involving 12 adult volunteers, ketorolac tromethamine tablets were co-administered with a single-dose of 25 mg *warfarin*, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine dosed IV or IM was given with two doses of 5000 U of *heparin* to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored.

The effects of warfarin and NSAIDs, in general, on GI bleeding are synergistic, such that the users of both drugs together have a risk of serious GI bleeding higher than the users of either drug alone.

Aspirin
When ketorolac tromethamine is administered with aspirin, its protein binding is reduced, although the clearance of free ketorolac tromethamine is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ketorolac tromethamine and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics
Clinical studies, as well as post-marketing observations, have shown that ketorolac tromethamine can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Probenecid
Concomitant administration of ketorolac tromethamine tablets and *probenecid* resulted in decreased clearance and volume of distribution of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine tablets and probenecid is contraindicated.

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

ACE Inhibitors/Angiotension II Receptor Antagonists
Concomitant use of *ACE inhibitors and/or angiotension II receptor antagonists* may increase the risk of renal impairment, particularly in volume-depleted patients.
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors and/or angiotension II receptor antagonists. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors and/or angiotension II receptor antagonists.

Antiepileptic Drugs
Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and *antiepileptic drugs* (phenytoin, carbamazepine).

Psychoactive Drugs
Hallucinations have been reported when ketorolac tromethamine was used in patients taking *psychoactive drugs* (fluoxetine, thiothixene, alprazolam).

Pentoxifylline
When ketorolac tromethamine is administered concurrently with pentoxifylline, there is an increased tendency to bleeding.

Nondepolarizing Muscle Relaxants

In post-marketing experience there have been reports of a possible interaction between ketorolac tromethamine IV/IM and *nondepolarizing muscle relaxants* that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin re-uptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administered concomitantly with SSRIs.

4.6 Pregnancy and lactation

Teratogenic effects. Pregnancy Category C

In late pregnancy, as with other NSAIDs, ketorolac tromethamine should be avoided because it may cause premature closure of the ductus arteriosus.

Results of various studies did not reveal evidence of teratogenicity to the fetus. However, animal reproduction studies are not always predictive of human response.

Nonteratogenic Effects

Because of the known effects of non-steroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

There are no adequate and well controlled studies of ketorolac tromethamine in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The use of ketorolac tromethamine 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.

Nursing Mothers

Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is contraindicated.

Exercise caution when ketorolac is administered to a nursing woman. Available information has not shown any specific adverse events in nursing infants; however, instruct patients to contact their infant's health care provider if they note any adverse events.

4.7 Effects on ability to drive and use machines

Some patients may experience dizziness, drowsiness, visual disturbances, headaches, vertigo, insomnia or depression with the use of ketorolac. If patients experience these, or other similar undesirable effects, they should not drive or operate machinery.

4.8 Undesirable effects

Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure. These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

In patients taking ketorolac tromethamine or other NSAIDs in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

Gastrointestinal (GI) experiences including:		
Abdominal Pain *	Constipation/Diarrhea	Dyspepsia*
Flatulence	GI Fullness	GI Ulcers (gastric/duodenal)
Gross Bleeding/Perforation	Heartburn	Nausea*
Stomatitis	Vomiting	
Other experiences:		
Abnormal Renal Function	Anaemia	Dizziness
Drowsiness	Edema	Elevated Liver Enzymes
Headaches*	Hypertension	Increased Bleeding Time
Injection Site Pain	Pruritus	Purpura
Rashes	Tinnitus	Sweating

*Incidence greater than 10%

Additional adverse experiences reported occasionally (<1% in patients taking ketorolac tromethamine or other NSAIDs in clinical trials) include:

Body as a Whole: fever, infections, sepsis

Cardiovascular: congestive heart failure, palpitation, pallor, tachycardia, syncope

Dermatologic: alopecia, photosensitivity, urticaria

Gastrointestinal: anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, rectal bleeding

Hemic and Lymphatic: ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia

Metabolic and Nutritional: weight change

Nervous System: abnormal dreams, abnormal thinking, anxiety, asthenia, confusion, depression, euphoria, extrapyramidal symptoms, hallucinations, hyperkinesis, inability to concentrate, insomnia, nervousness, paresthesia, somnolence, stupor, tremors, vertigo, malaise

Reproductive, female: infertility

Respiratory: asthma, cough, dyspnea, pulmonary edema, rhinitis

Special Senses: abnormal taste, abnormal vision, blurred vision, hearing loss

Urogenital: cystitis, dysuria, haematuria, increased urinary frequency, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure, urinary retention

Other rarely observed reactions (reported from post-marketing experience in patients taking ketorolac tromethamine or other NSAIDs) are:

Body as a Whole: angioedema, death, hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema, myalgia

Cardiovascular: arrhythmia, bradycardia, chest pain, flushing, hypotension, myocardial infarction, vasculitis

Dermatologic: exfoliative dermatitis, erythema multiforme, Lyell's syndrome, bullous reactions including Stevens - Johnson syndrome and toxic epidermal necrolysis

Gastrointestinal: acute pancreatitis, liver failure, ulcerative stomatitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease)

Hemic and Lymphatic: agranulocytosis, aplastic anaemia, haemolytic anaemia, lymphadenopathy, pancytopenia, postoperative wound hemorrhage (rarely requiring blood transfusion)

Metabolic and Nutritional: hyperglycaemia, hyperkalaemia, hyponatremia

Nervous System: aseptic meningitis, convulsions, coma, psychosis

Respiratory: bronchospasm, respiratory depression, pneumonia

Special Senses: conjunctivitis

Urogenital: flank pain with or without haematuria and/or azotemia, haemolytic uremic syndrome

4.9 Overdose

Symptoms and Signs

Symptoms following acute NSAIDs overdoses are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment

Patients should be managed by symptomatic and supportive care following a NSAIDs overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 g to 100 g in adults, 1 g/kg to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large oral overdose (5 to 10 times the usual dose). Forced diuresis, alkalization of urine, hemodialysis or hemoperfusion may not be useful due to high protein binding.

Single overdoses of ketorolac tromethamine 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, Acetic acid derivatives and related substances, ATC code: M01AB15

Mechanism of action

The primary mechanism of action responsible for ketorolac's anti-inflammatory, antipyretic and analgesic effects is the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX). Ketorolac is a non-selective COX inhibitor.

Pharmacodynamic effects

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models. The mechanism of action of ketorolac, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties. The peak analgesic effect of ketorolac tromethamine occurs within 2 to 3 hours and is not

statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine is in the duration of analgesia.

5.2 Pharmacokinetic properties

Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity.

The pharmacokinetics of ketorolac tromethamine, following oral doses of ketorolac tromethamine tablets, is compared in Table 1.

Linear Kinetics

In adults, following administration of single oral dose of ketorolac tromethamine in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in adults, following single or multiple recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Absorption

Ketorolac tromethamine is 100% absorbed after oral administration (see Table 1). Oral administration of ketorolac tromethamine after a high-fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about one hour. Antacids did not affect the extent of absorption.

Distribution

The mean apparent volume (V_d) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single-dose data. The ketorolac tromethamine racemate has been shown to be highly protein bound (99%). Nevertheless, plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations. Ketorolac tromethamine is excreted in human milk.

Metabolism

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Excretion

The principal route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. S-enantiomer is cleared approximately 2 times faster than the R-enantiomer and the clearance is independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S-form in humans.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

Kinetics in Special Populations

Geriatric Patients

Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years). There was little difference in the C for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03).

Pediatric Patients
Limited information is available regarding the pharmacokinetics of dosing of ketorolac tromethamine in the pediatric population. Following a single intravenous bolus dose of 0.5 mg/kg in 10 children 4 to 8 years old, the half-life was 5.8 ± 1.6 hours, the average clearance was 0.042 ± 0.01 L/hr/kg, the volume of distribution during the terminal phase (V_d) was 0.34 ± 0.12 L/kg and the volume of distribution at steady state (V_d) was 0.26 ± 0.08 L/kg. The volume of distribution and clearance of ketorolac in pediatric patients was higher than those observed in adult subjects (see Table 1). There are no pharmacokinetic data available for administration of ketorolac tromethamine by the IM route in pediatric patients.

Renal Insufficiency
Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r = 0.5).

In patients with renal disease, the AUC of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC_∞-ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects.

Hepatic Insufficiency
There was no significant difference in estimates of half-life, AUC and C in seven patients with liver disease compared to healthy volunteers. Race Pharmacokinetic differences due to race have not been identified.
Table 1: Approximate Average Pharmacokinetic Parameters (Mean ± SD) Following Oral, Dose of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	**Oral 10 MG***
Bioavailability (extent)	100%
T_{max}[1] (min)	44 ± 34
C_{max}[2] (mcg/mL) [single dose]	0.87 ± 0.22
C_{max} (mcg/mL) [steady state q.i.d.]	1.05 ± 0.26§
C_{min}[3] (mcg/mL) [steady state q.i.d.]	0.29 ± 0.07§
C_{ave}[4] (mcg/mL) [steady state q.i.d.]	0.59 ± 0.20§
VD[5] (L/kg)	0.175 ± 0.039

% Dose metabolized = <50
% Dose excreted in feces = 6
% Dose excreted in urine = 91
% Plasma protein binding = 99
1 Time-to-peak plasma concentration
2 Peak plasma concentration
3 Trough plasma concentration
4 Average plasma concentration
5 Volume of Distribution
*Derived from PO pharmacokinetic studies in 77 normal fasted volunteers

§Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed Cmax and Tmax data..

5.3 Preclinical safety data

Non-clinical data

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, Preclinical results were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use, 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Microcrystalline Cellulose, Maize Starch, Croscarmellose Sodium, Dibasic Calcium Phosphate, Magnesium Stearate, Purified water

Film-coat: Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose (HPMC) 5cps, Polyethylene Glycol 400, Propylene Glycol, Titanium Dioxide, Purified Talc, Isopropyl Alcohol, Methylene Chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

Strip pack (Alu/Alu) of 10 tablets. Such 2 strip packed in a carton with leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Applicant/Supplier

Cadila Pharmaceuticals Limited,
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Dist.: Ahmedabad, Gujarat state, India.

8 Marketing Authorization number(S)

FDB/SD.153-4258

9 Date of first authorization/renewal of the authorization

24/04/2015

10 Date of revision of the text

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