PRODUCT MONOGRAPH

# NOVO–KETOROLAC

(ketorolac tromethamine)

10 mg Tablets

NSAID Analgesic Agent

Novopharm Limited
Toronto, Canada

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**Control Number 112565**

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(ketorolac tromethamine)

10 mg Tablets

## THERAPEUTIC CLASSIFICATION

NSAID Analgesic Agent

## ACTION AND CLINICAL PHARMACOLOGY

NOVO-KETOROLAC (ketorolac tromethamine) is a non-steroidal anti-inflammatory drug (NSAID) that has analgesic activity. It is considered to be a peripherally acting analgesic. It is thought to inhibit the cyclo-oxygenase enzyme system, thereby inhibiting the synthesis of prostaglandins. At analgesic doses it has minimal anti-inflammatory and antipyretic activity.

The peak analgesic effect occurs at 2 to 3 hours post-dosing with no evidence of a statistically significant difference over the recommended dosage range. The greatest difference between large and small doses of administered ketorolac is in the duration of analgesia.

Following oral administration, ketorolac tromethamine is rapidly and completely absorbed, and pharmacokinetics are linear following single and multiple dosing. Steady state plasma levels are achieved after one day of q.i.d. dosing.

Peak plasma concentrations of 0.7 to 1.1 µg/mL occurred at 44 minutes following a single oral dose of 10 mg. The terminal plasma elimination half-life ranged between 2.4 and 9 hours in healthy adults, while in the elderly subjects (mean age: 72 years) it ranged between 4.3 and 7.6 hours. A high fat meal decreased the rate but not the extent of absorption of oral ketorolac tromethamine, while antacid had no effect.

In renally impaired patients there is a reduction in clearance and an increase in the terminal half-life of ketorolac tromethamine (See Table 1).

Table 1 - The Influence of Age, Liver and Kidney Function on the Clearance and Terminal Half-Life of Oral[1] 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) |

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

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

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

A comparative, two-way single dose bioavailability study was performed on two ketorolac tromethamine 10 mg tablet formulations, Novo-Ketorolac and Toradol®. The pharmacokinetic data calculated for ketorolac tromethamine in the Novo-Ketorolac and Toradol® tablet formulations is tabulated below:

Pharmacokinetic Indices for Ketorolac Tromethamine:

| | Geometric Mean<br>Arithmetic Mean (CV) | | |
|---|---|---|---|
| | Novo-Ketorolac<br>1 X 10 mg | Toradol®**<br>1 X 10 mg | Percentage of<br>Toradol® |
| $AUC_T$<br>(ng.h/mL) | 2643.32<br>2721.32 (25) | 2635.29<br>2715.33 (25) | 100 |
| $AUC_I$<br>(ng.h/mL) | 2816.92<br>2899.08 (25) | 2819.07<br>2899.32 (24) | 100 |
| $C_{max}$<br>(ng/mL) | 899.47<br>912.36 (17) | 838.27<br>863.66 (25) | 107 |
| $T_{max}$*<br>(h) | 0.60 (0.13) | 0.81 (0.36) | - |
| $T_{1/2}$*<br>(h) | 3.46 (0.17) | 3.67 (0.69) | - |

*For the Tmax and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
** Toradol® 10 mg Tablets (Syntex Inc., Canada)

## INDICATIONS AND CLINICAL USE

NOVO–KETOROLAC (ketorolac tromethamine) is indicated for the short-term management of mild to moderately severe pain, including post-surgical pain (such as general, orthopedic and dental surgery), acute musculoskeletal trauma pain and post-partum uterine cramping pain.

## CONTRAINDICATIONS

### Hypersensitivity

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

### Gastrointestinal:

NOVO-KETOROLAC should not be used in patients with suspected or confirmed peptic ulcer disease, gastrointestinal bleeding or perforation, or active inflammatory disease of the gastrointestinal system or in patients who have a history of these disorders.

Severe and fatal reactions have occurred in such individuals.

Renal Impairment:

NOVO-KETOROLAC is contraindicated in patients with moderate to severe renal impairment or in patients at risk for renal failure due to volume depletion.

Hemorrhagic Risk:

NOVO-KETOROLAC is contraindicated immediately before any major surgery, and is contraindicated intraoperatively when hemostasis is critical because of the increased risk of bleeding. NOVO-KETOROLAC is also contraindicated in patients with coagulation disorders, postoperative patients with high hemorrhagic risk or incomplete hemostasis, and in patients with suspected or confirmed cerebrovascular bleeding.

Obstetrics:

NOVO-KETOROLAC is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.

Concomitant Medications:

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

## WARNINGS

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

The most serious risks associated with NSAIDs including NOVO-KETOROLAC are:

### Gastrointestinal Ulcerations, Bleeding and Perforation

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

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

Post-marketing experience with ketorolac tromethamine suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding, and perforation in the elderly, and most spontaneous reports of fatal gastrointestinal events are in the aged population.

THE LONG-TERM USE OF NOVO-KETOROLAC IS NOT RECOMMENDED.

Renal Toxicity

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

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

Fluid Retention and Edema

Fluid retention, edema, NaCl retention, oliguria, elevations of serum urea nitrogen and creatinine have been observed in patients treated ketorolac tromethamine. Therefore, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be considered. NOVO-KETOROLAC should be used with caution in patients

with cardiac decompensation, hypertension or other conditions which cause a predisposition to fluid retention.

Hemorrhage

NOVO-KETOROLAC is contraindicated in patients who have coagulation disorders. If NOVO-KETOROLAC is to be administered to patients who are receiving drug therapy that interferes with hemostasis, careful observation is advised.

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

Hypersensitivity Reactions

The possibility of severe or fatal hypersensitivity reactions should be considered, even for patients with no known history of previous exposure or hypersensitivity to ketorolac or other NSAIDs. As with other NSAIDs, patients should be questioned for history of allergy to NSAIDs or ASA or for the syndrome consisting of nasal polyps, ASA allergy and asthma before prescribed NOVO-KETOROLAC. Asthmatic patients with triad asthma (the syndrome of nasal polyps, asthma and hypersensitivity to ASA or other NSAIDs) may be at particular risk for severe hypersensitivity reactions.

Use in Pregnancy and Lactation

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

Use in Children

Safety and efficacy in children have not been established. Therefore, NOVO-KETOROLAC is not recommended for use in children under age 16.

Use in the Elderly

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

## PRECAUTIONS

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

Gastrointestinal Effects

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

Patients taking any NSAID including ketorolac tromethamine should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or

gastrointestinal bleeding. These reactions can occur at any time during the treatment. If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding occurs, ketorolac tromethamine should be discontinued and appropriate treatment instituted with close patient monitoring.

Hepatic Effects

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

Hematologic Effects

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

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

Infection

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

## DRUG INTERACTIONS

### Protein Binding

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

### Anticoagulant Therapy

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

The *in vitro* binding of warfarin to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs. 99.3%) at plasma concentrations of 5 to10 μg/mL.

Digoxin

Ketorolac tromethamine does not alter digoxin protein binding.

Salicylates

*In vitro* studies indicated that, at therapeutic concentrations of salicylates (300 μg/mL), the binding of ketorolac tromethamine was reduced from approximately 99.2% to 97.5% representing a potential two-fold increase in unbound ketorolac plasma levels.

Enzyme Induction

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

Probenecid

Concomitant administration of ketorolac tromethamine and probenecid results in the decreased clearance of ketorolac and a significant increase in ketorolac plasma levels (approximately three-fold increase) and terminal half-life (approximately two-fold increase). The concomitant use of NOVO-KETOROLAC and probenecid is, therefore, contraindicated.

Furosemide

Ketorolac tromethamine reduces the diuretic response to furosemide by approximately 20% in normovolemic subjects.

Lithium

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

Methotrexate

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

ACE Inhibitors

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

## ADVERSE EVENTS

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.

**Musculo-skeletal System**: Myalgia, arthralgia

**Skin & 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 and Nutritional Disorder**: Edema

Incidence 1% or Less:

**Digestive System**: Eructation, stomatitis, vomiting, anorexia, duodenal ulcer, gastritis, gastrointestinal hemorrhage, 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 and Nutritional Disorder**: Weight gain, alkaline phosphatase increase, BUN increased, excessive thirst, generalized edema, hyperuricemia

**Skin & Appendages**: Pruritus, rash, burning sensation skin

**Body as a Whole**: Asthenia, pain, back pain, face edema, hernia

**Musculo-skeletal System**: Arthralgia, myalgia, joint disorder

**Cardiovascular System**: Chest pain, chest pain substernal, migraine

**Respiratory System**: Dyspnea, asthma, epistaxis

**Urogenital System**: Hematuria, increased urinary frequency, oliguria, polyuria

**Hemic & Lymphatic:** Anemia, purpura

**Postmarketing Experience**

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

**Renal Events**: acute renal failure, flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome, urinary retention.

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

**Gastrointestinal Events**: gastrointestinal hemorrhage, peptic ulceration, gastrointestinal perforation, pancreatitis, melena.

**Hematologic Events**: postoperative wound hemorrhage, rarely requiring blood transfusion (see PRECAUTIONS), thrombocytopenia, epistaxis, leukopenia

**Central Nervous System**: Convulsions, abnormal dreams, hallucinations, hyperkinesia, hearing loss, aseptic meningitis, extrapyramidal symptoms.

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

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

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

**Body as Whole**: infection

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

## DOSAGE AND ADMINISTRATION

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

Oral: The usual oral dose of NOVO-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.

Patients Under 50 kg, Over Age 65 years, or With Less Severe Pain at Baseline:

**Oral**: The lowest effective dose is recommended.

**Impaired Renal Function**: NOVO-KETOROLAC is not recommended for patients with moderate to severe renal impairment.

Conversion from Parenteral to Oral Therapy:

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

When NOVO-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.

## PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

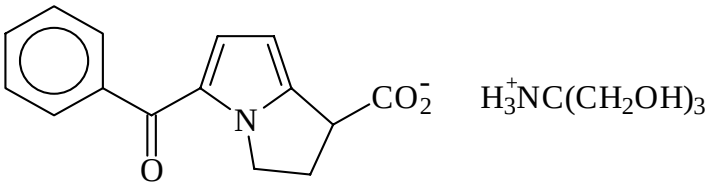
Proper Name: ketorolac tromethamine

Chemical Name: (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol.

Structural Formula:

Molecular Formula: $C_{19}H_{24}N_2O_6$ 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, dichlormethane, toluene, ethylacetate, dioxane, hexane, butanol and acetonitrile. The pH of a 1% (w/v) solution in distilled water is 5.7 - 6.7.



Stability and Storage Recommendations:

Store between 15–30°C and protect from light. Unit dose strips should be stored between 15-25°C and protected from high humidity and light.

## AVAILABILITY OF DOSAGE FORMS

NOVO–KETOROLAC (ketorolac tromethamine) is available as:

10 mg – White, round, biconvex, film coated tablet, embossed N on one side and 10 on the other side.

Supplied: Bottles of 100, 500, and 1000 and in boxes of 100 as unit dose strips.

# INFORMATION FOR THE PATIENT

## NOVO-KETOROLAC TABLETS

### How To Make NOVO-KETOROLAC Work Best For You

Your doctor has decided that NOVO-KETOROLAC (ketorolac tromethamine) is the best treatment for you. As you take your NOVO-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 NOVO-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 NOVO-KETOROLAC?

- NOVO-KETOROLAC tablets contain ketorolac tromethamine, a member of the class of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs).

- NOVO-KETOROLAC tablets are used for the short-term relief of pain including pain that occurs following surgery (such as general, orthopedic and dental surgery), and postpartum uterine cramping pain. It is also used for pain relief following injuries.

**How Does NOVO-KETOROLAC Work?**

NOVO-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 NOVO-KETOROLAC Be Taken?**

You should take NOVO-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.

The usual oral dose of NOVO-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.

NOVO-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.

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

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

**How Long Does It Take Before NOVO-KETOROLAC Begins To Work?**

Some people are able to feel improvement in their symptoms right away; for others, improvement may take up to 1 day. By the end of 1 day, if NOVO-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.

**Who should not use NOVO-KETOROLAC?**

- Do not use NOVO-KETOROLAC if you are sensitive or allergic to ketorolac (NOVO-KETOROLAC) or products containing acetysalicylic acid (ASA), or other salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs). Allergic reactions may include runny nose, difficulty breathing with wheezing, swelling, skin rashes or hives. NSAIDs include products such as diclofenac, diflunisal, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, naproxen sodium, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid or tolmetin.

- 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.
- Do not use NOVO-KETOROLAC if you have an ulcer or active inflammatory disease of the stomach or intestines. If you have a history of stomach upset, tell your doctor. All NSAIDs may aggravate your problem and sometimes even cause bleeding or ulcers in your stomach

or intestines. These complications can sometimes be severe and occasional fatalities have been reported with all drugs of this class.

- NOVO-KETOROLAC should not be used by children under 16 years of age, except as recommended by a doctor or dentist.

- Do not use NOVO-KETOROLAC if you intend to become pregnant, are pregnant or breast feeding.

- Do not use NOVO-KETOROLAC if you are taking ASA, products containing ASA or other NSAIDs, e.g., drugs to relieve symptoms of arthritis.

**Consult your doctor before taking NOVO-KETOROLAC if you:**

- are allergic (see definition above) to NOVO-KETOROLAC tablets or other related medicines of the NSAID group such as ASA, diclofenac, diflunisal, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, naproxen sodium, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tiaprofenic acid, tenoxicam or tolmetin;
- have a history of stomach upset, ulcers, or liver or kidney diseases;
- have high blood pressure or heart failure;
- are pregnant or intend to become pregnant while taking this medicine;
- are breast feeding;
- are taking any other medicine (either prescription or non-prescription);

- have any other medical problem.

**Does NOVO-KETOROLAC Have Any Side Effects?**

Any medication can cause side effects; this is true for acetylsalicylic acid (ASA) and all of the nonsteroidal anti-inflammatory drugs. Elderly (generally over 65) patients may be more sensitive to the effects of all NSAIDs including NOVO-KETOROLAC.

Relatively common unwanted side effects of all nonsteroidal anti-inflammatory drugs are heartburn, abdominal pain, nausea, diarrhea, constipation and so forth. You may take NOVO-KETOROLAC with meals or a snack to reduce discomfort of this type but this may delay the beginning of pain relief.

All NSAIDs may aggravate gastrointestinal problems and sometimes even cause bleeding or ulcers in your stomach or intestines. These complications can sometimes be severe and occasional fatalities have been reported with all drugs of this class.

**Contact your doctor immediately if you experience any of these symptoms:**

- bloody or black tarry stools;
- shortness of breath, wheezing, and trouble in breathing or tightness in the chest;
- skin rash, swelling, hives or itching;
- indigestion, nausea, vomiting, stomach pain or diarrhea;
- yellow discoloration of the skin or eyes, with or without fatigue;
- any changes in the amount or color of your urine (as dark red or brown);
- swelling of the feet or lower legs;
- blurred vision or any visual disturbance.

Other effects that have been reported infrequently include headache, drowsiness, dizziness, depression, and ringing in the ears. These reactions usually do not pose a serious problem, and most people can continue treatment. More rarely, visual or hearing disturbances and blood disorders have occurred. **Contact your doctor if you experience any problems.** Almost all of the side effects experienced with NOVO-KETOROLAC stop when the medication is stopped.

**Are There Any Special Do's And Don'ts About Taking NOVO-KETOROLAC?**

**DO's:**

Do tell your doctor and pharmacist about any other medications you take, both prescription and nonprescription. This is important because some drugs can interact with each other and produce undesirable effects.

Do tell your doctor if you have an ulcer, liver disease, kidney disease or history of any stomach problems.

Do be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or light-headed after taking NOVO-KETOROLAC.

Do check with your doctor if:

you are not getting relief

or

you have any problems while taking NOVO KETOROLAC.

Do tell your physician if you are pregnant or are planning to become pregnant.

**DON'TS:**

Don't take NOVO-KETOROLAC if you are breast feeding. The drug does pass into the milk of nursing women.

Don't take ASA (acetylsalicylic acid), ASA-containing products or other NSAIDs, e.g., drugs to relieve symptoms of arthritis while taking NOVO-KETOROLAC unless specifically directed to do so by a physician. Consult your doctor or pharmacist if you are unsure what your product contains. A partial list of brand name products containing ASA, NSAIDs and Ibuprofen is included at the end of this leaflet.

Don't take NOVO-KETOROLAC if you are allergic to it, or if you have had an allergic-type reaction to ASA or to any other drug used for pain relief or arthritis.

Don't take NOVO-KETOROLAC if you have a stomach ulcer, or active inflammatory disease of the stomach or intestine.

| ASA-Containing OTC Brands | NSAID-Containing Brands | Ibuprofen-Containing Brands |
|---|---|---|
| Anacin, Bufferin, Aspirin, Alka-selzer, 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 | Advil, Actiprofen, Nuprin, Medipren, Motrin IB |

# PHARMACOLOGY

## Animal Pharmacology

### Analgesic Properties

In tests utilizing an underlying inflammatory state, ketorolac was found to be a potent orally active analgesic agent. In mice, administered with oral or subcutaneous doses ranging from 0.05-2.25 mg/kg, the drug was 250-350 times more potent than aspirin in inhibiting phenylquinone-induced writhing. Similar tests conducted in rats receiving 0.03-1.0 mg/kg p.o., revealed that ketorolac was 180 times as potent as aspirin in inhibiting the writhing response.

In rats having adjuvant-induced arthritis, ketorolac administered orally was 400-800 times more potent than aspirin and twice as potent as naproxen in alleviating pain. Ketorolac tromethamine 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 compound did not increase the pain threshold of the non-inflamed paw nor did it display any analgesic activity in the mouse hot plate test. From this evidence, it can be concluded that ketorolac is not a morphine like compound.

### Anti-inflammatory Properties

Ketorolac exhibited 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 potent as phenylbutazone in inhibiting carrageenan-induced paw inflammation when administered orally. This difference in activity is due to the compound.

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

Thymic involution was not produced when ketorolac was administered to rats at a dose of 2 mg/kg/day p.o., for 6 days. This shows 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 conclusions were further confirmed by the dose-related anti-inflammatory activity in adrenalectomized rats.

Antipyretic Properties

Ketorolac had 20 times the antipyretic potency of aspirin when administered orally to yeast-infected rats in doses ranging from 0.1-2.7 mg/kg.

Prostaglandin Inhibition

Current evidence in the literature indicates that the anti-inflammatory, analgesic and antipyretic activities of non-steroidal anti-inflammatory drugs (NSAIDs) are due to their ability to inhibit prostaglandin biosynthesis.

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

Platelet Effects

In *in vitro* studies, ketorolac was 37 times as effective 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 provoked by thromboxane A2.

Central Nervous System Effects

In mice, intraperitoneal administration of ketorolac at doses up to 300 mg/kg had minimal behavioural effects. At doses exceeding this level, depression of normal behaviour was seen.

No significant central nervous system (CNS) activity was produced by ketorolac. No anticonvulsant activity was observed in mice in the maximal electroshock test nor were there any signs of inhibition of pentylenetetrazol-induced seizures in mice or rats.

In mice, hexobarbital-induced sleep time was unchanged by ketorolac, indicating 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 unaltered.

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. Ketorolac inhibited cardiovascular responses to adrenaline, nor-adrenaline, tyramine, phenylephrine and bilateral carotid artery occlusion, suggesting mild alpha-adrenoreceptor blocking activity.

Bronchial Effects

In guinea pigs, doses of 0.01-10 mg/kg ketorolac administered intravenously was unsuccessful in blocking histamine - or methacholine-induced bronchoconstriction.

In the rat, the compound blocked methacholine-induced airway constriction ($ED_{50}$=0.5 mg/kg).

Gastric Effects

Ketorolac at doses of 0.1 and 1.0 mg/kg p.o. in rats did not have a significant effect on either the gastric juice volume or the total mEq of hydrogen ions secreted in response to histamine stimulation. Furthermore, like other NSAIDs, both the acid and the tromethamine salt of ketorolac had a similar tendency to cause gastrointestinal erosions in rats independent of the route of administration.

Pharmacokinetics

A series of trials 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 was later selected for development due to its more rapid and complete absorption.

Ketorolac tromethamine was rapidly (Tmax ranged from 0.25 -1.5 hr) and completely absorbed after oral and i.m. dose in animals (>87%) and humans (>99%). Linear pharmacokinetics were observed in man following single or multiple intramuscular doses. Steady state plasma levels are achieved after dosing every 6 hours for one day. Clearance was unchanged 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 calculated following intravenous dosing ranged from 0.09 L/kg in mice to 0.38 L/kg in rats; in humans it averaged 0.15 L/kg. Total plamsa clearance ranged form 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 kidney had the highest levels and was the only organ which exceeded plasma levels at all time points (by about 50%). The lowest levels were found 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 by as much as four fold at all time points. In rabbits, however, milk concentrations were only about 12% of plasma concentrations.

Metabolism

*In vivo* and *in vitro* 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.

In humans, a moderate (about 20%) first pass metabolism was observed , while rabbits displayed 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. Radioactivity of ketorolac circulating in the plasma ranged from 79% in rabbits to 99% in mice and averaged 96% in humans. Conjugates of ketorolac were not detected in plasma in any significant amounts in any of the 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 primarily 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:

| Species | Route | LD50 (mg/kg) |
|---|---|---|
| Mouse | oral | approx. 400 |
| Mouse | oral+ | 529 (281-1540)* |
| Rat | oral | 112 (68-191)* |
| Rat | oral+ | 100-400 |
| Mouse | i.p. | > 400 |
| Mouse | i.p.+ | 473 (315-771)* |
| Rat | i.p. | 158 (101-248)* |
| Rat | i.p.+ | 100-400 |

* 95% confidence interval

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

Ketorolac administered at a dose of 200 mg/kg, p.o. in 1 male and 1 female cynomolgus monkey caused both monkeys to vomit after dosing. Diarrhea and anorexia were observed in the female 5 days after dosing. The male monkey gained weight while the female had weight loss. Both animals had decreased hemoglobin and hematocrit and survived the 2 week post dose period.

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

Sensitization:

A 0.1% solution of ketorolac tromethamine did not cause sensitization when tested in the guinea pig model.

Vein Irritation

Ketorolac tromethamine at a concentration of 10 mg/mL was injected intravenously 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 recorded microscopically in some animals that received the vehicle or drug formulations.

Subacute Toxicity:

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.

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

Hematologic parameters measured revealed decreased hemoglobin and hematocrit levels for groups receiving 4.0 or 16.0 mg/kg/day and elevated total leukocyte and neutrophil counts in the high dose group animals. No significant biological 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 treatment related pathological change was present in mice from other dose groups.

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

Intravenous

Rabbits and monkeys administered ketorolac tromethamine intravenously at doses of 0 (vehicle), 0.5, 1.25 or 2.5 mg/kg/day for 2 weeks did not show any clinically significant drug related effects.

Long- Term Toxicity:

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, a pattern of slightly lower body weight and lesser feed intake were seen in treated males and females relative to controls. No drug related ocular lesions were observed in animals.

Prior to the end 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 main 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. Renal inflammatory lesions at all dose levels were found especially in females. Histological tests revealed an apparent interruption of ovarian cyclic activity. 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.

The only significant change observed was a 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 observed in renal cortex which correlated with cortical pallor.

Two groups each with 5 male and 5 female cynomolgus monkeys were given a daily dose of 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 to be treatment related. No drug related differences were found in the clinical condition of the surviving animals. The males displayed a dose related decrease in RBC count,

hemoglobin, hematocrit, mean corpuscular hemoglobin and hemoglobin concentration. The females were not affected to the same degree as the males but did show slight 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. No change was detected in the BUN of the females, 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 include increased intertubular matrix in the papilla and intratubular mineralization in the cortical, medullary and papillary tubules. Animals given a 2 month period of recovery from dosing did not show any signs of morphologic damage.

These results indicate 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 tromethmine in their diet. A control group of 100 animals of each sex received the same diet without ketorolac. The study lasted 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 high dose males were found to have a generally lower body weight than that of the controls during the second half of the study. However, this effect was not seen 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 a decrease in food intake.

Histopathologic examinations found no indications in the incidence of any type of tumor. In the high dose group, enteritis, gastroenteropathy and peritonitis were observed which is to be expected sequelae to high doses of an NSAID.

The above evidence indicates a lack of carcinogenic effect of ketorolac tromethamine in the mouse.

Fifty Sprague-Dawley rats of either sex were used in a 24 month feeding study to evaluate the carcinogenic potential of ketorolac tromethamine. Each rat received in their diet either of 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.

The only treatment related change noted in the clinical condition was a reddish discolouration 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.

Although no difference in food intakes was found in the various groups, the body weights of the high dose group females were approximately 10% lower than the controls during the last 6 months of the study. The high dose males had decreased erythroid parameters, elevated platelet count and a higher incidence of blood in the urine specimens. Both males and females in the high dose group 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.

It was concluded that there was no carcinogenic effect of ketorolac tromethamine in rats.

Mutagenicity

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

Tests performed with and without mammalian microsomal activation found no indication of mutagenicity with the compound. 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 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 potential of F2 pups was also studied.

No drug-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 duration of gestation was significantly increased in the high-dose (P1 females) group (median 25 days) in comparison to the controls (median 22 days). A slight increase in the length of gestation (median 22.5 days) was recorded in the mid-dose group when compared to the controls. In the high-dose group only, decreased live litter sizes and survival indices were the main findings in comparison to the 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. In the low and mid-dose groups, the maternal care and lactation data were comparable with the controls. The clinical condition and body weights of surviving F1 pups were comparable among all the groups. No treatment-related effects were found in the postnatal behavioural and developmental assessment of the F1 pups. The reproductive performance of the F1 pups and the neonatal survival of their offspring (F2 pups) were comparable among the groups.

In summary, administration of ketorolac tromethamine in the diets of 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 administered ketorolac tromethamine once daily by gavage at doses of 0, 3.0, 6.0, or 9.0 mg/kg. Prior to mating with untreated females, males were dosed for 104 days and continued to be dosed through the 14 day mating period. Mating units consisted of one dosed male and two untreated females. Approximately half of the females with evidence of mating were sacrificed at midgestation while the other half were allowed to litter and raise their pups until 21 days postpartum.

No drug-related changes were noted in the clinical conditions of the males. Drug treatment did not affect body weight or food intake. There were no drug-related differences in the number of males leaving evidence of mating, the pre-coital interval, or in the number impregnating females.

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

No differences between the drug groups and the controls could be detected with respect to body weight, length of gestation, gestation index, lactation index, number of pups born alive and survival indices. In conclusion, the administration of ketorolac tromethamine by gavage to male rats prior to and during the mating period had no effects on male reproductive performance nor on 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 skeletal examination if possible.

A dose of 9.0 mg/kg/day of ketorolac tromethamine 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. Compared to the control group, the weight of male and female pups was also decreased at days 4 and 7 postpartum.

A dose of 4.8 mg/kg/day of ketorolac tromethamine 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 recorded at the two highest dose levels were expected for a drug of this class.

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

Teratology Studies:

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 another 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 day 15 of gestation; duodenal ulceration and peritonitis considered to be treatment related were observed. No embryotoxicity or embryolethality were seen. External and skeletal or visceral examinations of fetuses did not reveal any teratogenic changes that could be attributed to the treatment.

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 day 18 of gestation of undetermined cause. All other animals survived to the end of the study. In the high dose animals, a slight body weight loss was noted

along with a slight dose related reduction in food consumption during days 6 through 11 of gestation.

There were no statistically significant differences in the number of litters with malformations in any of the treated groups in comparison to the control group. For all groups the developmental and genetic variations in fetuses were comparable.

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