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■ PMS Black

Approved for FDA submission  
J. Strong 05/02/14

#### Geriatric Use (≥65 Years of Age)

Because ketorolac tromethamine may be cleared more slowly by the elderly (see **CLINICAL PHARMACOLOGY**) who are also more sensitive to the dose-related adverse effects of NSAIDs (see **WARNINGS – Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**), extreme caution and reduced dosages (see **DOSE AND ADMINISTRATION**) and careful clinical monitoring must be used when treating the elderly with ketorolac tromethamine.

#### ADVERSE REACTIONS

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 (see **Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION**). 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	anemia	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, hyperkinesia, 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, hematuria, increased urinary frequency, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure, urinary retention

Other rarely observed reactions (reported from postmarketing 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 (see **WARNINGS**), 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 anemia, hemolytic anemia, lymphadenopathy, pancytopenia, post operative wound hemorrhage (rarely requiring blood transfusion — see **Boxed WARNING, WARNINGS, and PRECAUTIONS**)

**Metabolic and Nutritional:** hyperglycemia, hyperkalemia, hyponatremia

**Nervous System:** aseptic meningitis, convulsions, coma, psychosis

**Respiratory:** bronchospasm, respiratory depression, pneumonia

**Special Senses:** conjunctivitis

**Urogenital:** flank pain with or without hematuria and/or azotemia, hemolytic uremic syndrome

#### Postmarketing Surveillance Study

A large postmarketing observational, nonrandomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (GI) bleeding was dose-dependent (see Tables 3A and 3B). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine (see Table 3A).

Table 3: Incidence of Clinically Serious G.I. Bleeding as Related to Age, Total Daily Dose, and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine Injection

Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

#### B. Adult Patients with History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25.0%

#### OVERDOSAGE

##### 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.

#### DOSE AND 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 oral ketorolac tromethamine is not to exceed 5 days. In adults, the use of oral ketorolac tromethamine is only indicated as continuation therapy to IV or IM dosing of ketorolac tromethamine. See package insert for ketorolac tromethamine tablets for transition from IV or IM dosing of ketorolac tromethamine (single- or multiple-dose) to multiple-dose oral ketorolac tromethamine.

**Note: Oral formulation should not be given as an initial dose.**

**Use minimum effective dose** for the individual patient.

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

#### KETOROLAC TROMETHAMINE INJECTION

Ketorolac tromethamine injection may be used as a single or multiple dose on a regular or "prn" schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine (see **WARNINGS – Renal Effects**). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

When administering ketorolac tromethamine injection, the IV bolus must be given over no less than 15 seconds. The IM administration should be given slowly and deeply into the muscle. The analgesic effect begins in ~30 minutes with maximum effect in 1 to 2 hours after dosing IV or IM. Duration of analgesic effect is usually 4 to 6 hours.

**Single-Dose Treatment: The following regimen should be limited to single administration use only**

##### IM Dosing

- Patients <65 years of age: One dose of 60 mg.
- Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 30 mg.

##### IV Dosing

- Patients <65 years of age: One dose of 30 mg.
- Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 15 mg.

#### Multiple-Dose Treatment (IV or IM)

- Patients <65 years of age: The recommended dose is 30 mg ketorolac tromethamine injection every 6 hours. The maximum daily dose for these populations should not exceed 120 mg.
- For patients ≥65 years of age, renally impaired patients (see **WARNINGS**), and patients less than 50 kg (110 lbs): The recommended dose is 15 mg ketorolac tromethamine injection every 6 hours. The maximum daily dose for these populations should not exceed 60 mg.

For breakthrough pain, do not increase the dose or the frequency of ketorolac tromethamine. Consideration should be given to supplementing these regimens with low doses of opioids "prn" unless otherwise contraindicated.

#### Pharmaceutical Information for Ketorolac Tromethamine Injection

Ketorolac tromethamine injection should not be mixed in a small volume (e.g., in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution.

**NOTE:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

#### HOW SUPPLIED

Ketorolac Tromethamine Injection, USP is supplied as follows:

NDC Number	Container Description	Concentration (mg/mL)	Fill Volume/ Container Size	Total Ketorolac Tromethamine (Per Container)
0409-3793-01	Single-Dose Glass Flitrop Vial	15 mg/mL	1 mL/2 mL	15 mg
0409-3795-01	Single-Dose Glass Flitrop Vial	30 mg/mL	1 mL/2 mL	30 mg
*0409-3796-01	Single-Dose Glass Flitrop Vial	30 mg/mL	2 mL/2 mL	60 mg

#### \*FOR IM USE ONLY.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

**Protect from light.**

Retain in carton until time of use.

#### Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

#### What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

**NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.** This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

**NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."**

**NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:**

- can happen without warning symptoms
- may cause death

**The chance of a person getting an ulcer or bleeding increases with:**

- taking medicines called "corticosteroids" and "anticoagulants"
- smoking
- drinking alcohol
- older age
- having poor health

**NSAID medicines should only be used:**

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

**What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

**NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:**

- different types of arthritis
- menstrual cramps and other types of short-term pain

**Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?**

**Do not take an NSAID medicine:**

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

**Tell your healthcare provider:**

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects.

**Keep a list of your medicines to show to your healthcare provider and pharmacist.**

- if you are pregnant.

**NSAID medicines should not be used by pregnant women late in their pregnancy.**

- if you are breastfeeding. **Talk to your doctor.**

#### What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

**Serious side effects include:**

- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including liver failure
- asthma attacks in people who have asthma

**Other side effects include:**

- heart attack
- diarrhea
- nausea
- stomach pain
- gas
- vomiting
- constipation
- heartburn
- dizziness

**Get emergency help right away if you have any of the following symptoms:**

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

**Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:**

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood

- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines.

Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

**Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.

- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

#### NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

\*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC label warns that long term continuous use may increase the risk of heart attack or stroke.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to [www.hospira.com](http://www.hospira.com) or call 1-800-615-0187.**

*This Medication Guide has been approved by the U.S. Food and Drug Administration.*

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Hospira, Inc., Lake Forest, IL 60045 USA



EN-3485

# Ketorolac Tromethamine Injection, USP

Rx only

FOR IV/IM USE (15 mg and 30 mg)  
FOR IM USE ONLY (60 mg)



#### WARNING

Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days in adults) management of moderately severe acute pain that requires analgesia at the opioid level. Oral ketorolac tromethamine is indicated only as continuation treatment following IV or IM dosing of ketorolac tromethamine, if necessary. The total combined duration of use of oral ketorolac tromethamine and ketorolac tromethamine injection should not exceed 5 days.

**Ketorolac tromethamine is not indicated for use in pediatric patients and it is NOT indicated for minor or chronic painful conditions. Increasing the dose of ketorolac tromethamine beyond the label recommendations will not provide better efficacy but will increase the risk of developing serious adverse events.**

#### GASTROINTESTINAL RISK

- Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Therefore, 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. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

#### CARDIOVASCULAR RISK

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS** and **CLINICAL STUDIES**).
- Ketorolac tromethamine is CONTRAINDICATED for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

#### RENAL RISK

- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see **WARNINGS**).

#### RISK OF BLEEDING

- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see **WARNINGS** and **PRECAUTIONS**).

**Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery.**

#### HYPERSENSITIVITY

- Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac tromethamine injection (see **CONTRAINDICATIONS** and **WARNINGS**). Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

#### INTRATHECAL OR EPIDURAL ADMINISTRATION

- Ketorolac tromethamine is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol content.

#### RISK DURING LABOR AND DELIVERY

- The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and inhibit uterine contractions.

#### CONCOMITANT USE WITH NSAIDs

- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving aspirin or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

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#### SPECIAL POPULATIONS

- Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs.) of body weight (see **DOSEAGE AND ADMINISTRATION**) and for patients with moderately elevated serum creatinine (see **WARNINGS**). Doses of ketorolac tromethamine injection are not to exceed 60 mg (total dose per day) in these patients.

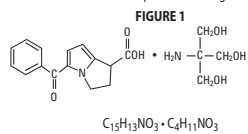
#### DOSEAGE AND ADMINISTRATION

##### Ketorolac Tromethamine Tablets

- Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine injection, and the combined duration of use of ketorolac tromethamine injection and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.
- The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine injection (maximum 120 mg) (see **DOSEAGE AND ADMINISTRATION**).

#### DESCRIPTION

Ketorolac Tromethamine Injection, USP is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (+)-5-benzyl-2,3-dihydro-1H-pyrrolo[1,2-b]pyridine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1), and the structural formula is presented in Figure 1.



Ketorolac tromethamine is a racemic mixture of (-)-S and (+)-R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a  $pK_a$  of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.40. Ketorolac Tromethamine Injection, USP is available for intravenous (IV) or intramuscular (IM) administration as: 15 mg in 1 mL (1.5%) and 30 mg in 1 mL (3%) in sterile solution; 60 mg in 2 mL (3%) of ketorolac tromethamine in sterile solution is available for IM administration only. The solutions contain 10% (w/v) alcohol, USP, and 6.68 mg, 4.35 mg, and 8.70 mg, respectively, of sodium chloride in sterile water. The pH range is 6.9 to 7.9 and is adjusted with sodium hydroxide and/or hydrochloric acid. The sterile solutions are clear and slightly yellow in color.

#### CLINICAL PHARMACOLOGY

##### Pharmacodynamics

Ketorolac tromethamine is a nonsteroidal 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 synthase 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 by either route is in the duration of analgesia.

##### Pharmacokinetics

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

##### Comparison of IV, IM and Oral Pharmacokinetics

The pharmacokinetics of ketorolac tromethamine, following IV, IM and oral doses of ketorolac tromethamine are compared in Table 1. In adults, the extent of bioavailability following administration of the ORAL and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

Pharmacokinetic Parameters (units)	Oral <sup>†</sup>		Intramuscular <sup>*</sup>		Intravenous Bolus <sup>‡</sup>	
	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T <sub>max</sub> <sup>1</sup> (min)	44±34	33±21**	44±29	33±21**	1.1±0.7**	2.9±1.8
C <sub>max</sub> <sup>2</sup> (mcg/mL) (Single-dose)	0.87±0.22	1.14±0.32**	2.42±0.68	4.55±1.27**	2.47±0.51**	4.65±0.96
C <sub>max</sub> (mcg/mL) (steady state qd)	1.05±0.26**	1.56±0.44**	3.11±0.87**	N/A <sup>††</sup>	3.09±1.17**	6.85±2.61
C <sub>min</sub> <sup>3</sup> (mcg/mL) (steady state qd)	0.29±0.07**	0.47±0.13**	0.93±0.26**	N/A	0.61±0.21**	1.04±0.35
C <sub>avg</sub> <sup>4</sup> (mcg/mL) (steady state qd)	0.59±0.2**	0.94±0.29**	1.88±0.59**	N/A	1.09±0.3**	2.17±0.59
V <sub>d</sub> <sup>5</sup> (L/kg)	0.175±0.039				0.210±0.044	

% Dose metabolized = <50  
% Dose excreted in urine = 91  
% Dose excreted in feces = 6  
% Plasma protein binding = 99  
<sup>1</sup>Time-to-peak plasma concentration

<sup>†</sup>Derived from PO pharmacokinetic studies in 77 normal fasted volunteers

<sup>\*</sup>Derived from IM pharmacokinetic studies in 54 normal volunteers

<sup>‡</sup>Derived from IV pharmacokinetic studies in 24 normal volunteers

<sup>††</sup>Not applicable because 60 mg IV is only recommended as a single dose

<sup>‡‡</sup>Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C<sub>max</sub> and T<sub>max</sub> data

#### Linear Kinetics

In adults, following administration of single ORAL, IM or IV doses 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 IM, IV or 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.

#### Distribution

The mean apparent volume (V<sub>d</sub>) 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 (see **PRECAUTIONS – Nursing Mothers**).

#### 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. A single-dose study with 10 mg ketorolac tromethamine (n = 9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time in each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined in Table 2 (see **CLINICAL PHARMACOLOGY – Kinetics in Special Populations**).

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.

#### Accumulation

Ketorolac tromethamine administered as an IV bolus, every 6 hours, for 5 days, to healthy subjects (n = 13), showed no significant difference in C<sub>max</sub> on Day 1 and Day 5. Trough levels averaged 0.29 mcg/mL (SD ± 0.13) on Day 1 and 0.55 mcg/mL (SD ± 0.23) on Day 6. Steady state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (geriatric, pediatric, renal failure patients, or hepatic disease patients).

#### 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) (see **Table 2**). There was little difference in the C<sub>max</sub> for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see **PRECAUTIONS – Geriatric Use**).

##### 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<sub>d</sub>) was 0.34 ± 0.12 L/kg and the volume of distribution at steady state (V<sub>dss</sub>) 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<sub>0-∞</sub> of each enantiomer doubled 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<sub>0-∞</sub> 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 (see **WARNINGS – Renal Effects**).

##### Hepatic Insufficiency

There was no significant difference in estimates of half-life, AUC<sub>0-∞</sub> and C<sub>max</sub> in 7 patients with liver disease compared to healthy volunteers (see **PRECAUTIONS – Hepatic Effects and Table 2**).

#### Race

Pharmacokinetic differences due to race have not been identified.

Table 2: The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-Life of Ketorolac Tromethamine (IM<sup>1</sup> and ORAL<sup>2</sup>) in Adult Populations

Type of Subjects	Total Clearance (L/h/kg) <sup>3</sup>		Terminal Half-life (in hours)	
	IM Mean (range)	ORAL Mean (range)	IM Mean (range)	ORAL Mean (range)
Normal Subjects IM (n = 54) mean age = 32, range = 18-60 Oral (n = 77) mean age = 32, range = 20-60	0.023 (0.010-0.046)	0.025 (0.013-0.050)	5.3 (3.5-9.2)	5.3 (2.4-9)
Healthy Elderly Subjects IM (n = 13), Oral (n = 12) mean age = 72, range = 65-78	0.019 (0.013-0.034)	0.024 (0.018-0.034)	7 (4.7-8.6)	6.1 (4.3-7.6)
Patients with Hepatic Dysfunction IM and Oral (n = 7) mean age = 51, range = 43-64	0.029 (0.013-0.066)	0.033 (0.019-0.051)	5.4 (2.2-6.9)	4.5 (1.6-7.6)
Patients with Renal Impairment IM (n = 25), Oral (n = 9) serum creatinine = 1.9-5.0 mg/dL, mean age (IM) = 54, range = 35-71 mean age (Oral) = 57, range = 39-70	0.015 (0.005-0.043)	0.016 (0.007-0.052)	10.3 (5.9-19.2)	10.8 (3.4-18.9)
Renal Dialysis Patients IM and Oral (n = 9) mean age = 40, range = 27-63	0.016 (0.003-0.036)	–	13.6 (8.0-39.1)	–

<sup>1</sup>Estimated from 30 mg single IM doses of ketorolac tromethamine

<sup>2</sup>Estimated from 10 mg single oral doses of ketorolac tromethamine

<sup>3</sup>Liters/hour/kg

**IV-Administration:** In normal subjects (n=37), the total clearance of 30 mg IV-administered Ketorolac Tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours. (See **Kinetics in Special Populations** for use of IV dosing of ketorolac tromethamine in pediatric patients.)

#### CLINICAL STUDIES

##### Adult Patients

In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine IV as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q3h), required significantly less morphine (26% than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving ketorolac tromethamine IV plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

##### INDICATIONS AND USAGE

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

##### Geriatric Adult Patients

Ketorolac tromethamine is 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 IV or IM dosing of ketorolac tromethamine, and oral ketorolac tromethamine is to be used only as continuation therapy, if necessary.

The total combined duration of use of ketorolac tromethamine injection and oral ketorolac tromethamine 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 (see **WARNINGS, PRECAUTIONS, DOSEAGE AND ADMINISTRATION, and ADVERSE REACTIONS**). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

Ketorolac tromethamine injection has been used concomitantly with morphine and meperidine and has shown an opioid-sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the ketorolac tromethamine injection dosage range with low doses of narcotics *pm*, unless otherwise contraindicated. Ketorolac tromethamine injection and narcotics should not be administered in the same syringe (see **DOSEAGE AND ADMINISTRATION – Pharmaceutical Information for Ketorolac Tromethamine Injection**).

##### CONTRAINDICATIONS

(see also **Boxed WARNING**) 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, anaphylactoid reactions to NSAIDs have been reported in such patients (see **WARNINGS – Anaphylactoid Reactions, and PRECAUTIONS – Pre-existing Asthma**).

Ketorolac tromethamine is contraindicated as prophylactic analgesic before any major surgery. Ketorolac tromethamine is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Ketorolac tromethamine is contraindicated in patients with advanced renal impairment or in patients at risk for renal failure due to volume depletion (see **WARNINGS** for correction of volume depletion).

Ketorolac tromethamine 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.

Ketorolac tromethamine inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see **WARNINGS and PRECAUTIONS**).

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. Ketorolac tromethamine injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.

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 does increase the risk of serious GI events (see **Gastrointestinal Effects– Risk of Ulceration, Bleeding, and Perforation**). 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 (see **CONTRAINDICATIONS**).

**WARNINGS** (See also **Boxed WARNING**) The total combined duration of use of oral ketorolac tromethamine and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric 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 gastrointestinal (GI) bleeding. Ketorolac tromethamine can cause serious 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, and duration of treatment with ketorolac tromethamine. Do not use ketorolac tromethamine for more than five 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.

**Hemorrhage** 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 (2500-5000 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 postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the peri-operative use of IV or IM dosing of ketorolac tromethamine. Therefore, peri-operative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see **PRECAUTIONS**).

##### 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 pre-treatment 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 (see **CLINICAL PHARMACOLOGY**). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see **DOSEAGE AND ADMINISTRATION**) 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 (see **CONTRAINDICATIONS**). 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 known prior exposure 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 (see **CONTRAINDICATIONS and PRECAUTIONS – Pre-existing Asthma**). 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 three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which may be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or 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 does increase the risk of serious GI events (see **Gastrointestinal Effects– Risk of Ulceration, Bleeding, and Perforation**). 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 (see **CONTRAINDICATIONS**).

**Hypertension** NSAIDs, including ketorolac tromethamine, can lead to onset of new hypertension or worsening of pre-existing 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** Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension or similar conditions.

##### 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 or any other sign of hypersensitivity.

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

**PRECAUTIONS**

##### 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 Effects** 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 three 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 Effects

Anemia 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 hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. 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.

**Pre-existing 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 nonsteroidal 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 pre-existing 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 (see **Boxed WARNING, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections), instruct patients to seek medical advice if they develop treatment-related adverse events, and advise patients not to give oral ketorolac tromethamine to other