Ketorolac Tromethamine Injection, USP

FOR INTRAVENOUS/INTRAMUSCULAR USE (15 mg and 30 mg) FOR INTRAMUSCULAR 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 intravenous or intramuscular dosing of ketorolac tromethamine, if necessary. The total combined duration of use of oral ketorolad

sary. 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 pedi-atric 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 devel-oping serious adverse events.

### GASTROINTESTINAL RISK

Ketorolac tromethamine can cause peptic ulcers, gastro-intestinal 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 THROMBOTIC EVENTS

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (see WARNINGS and DEFOULTIONS) may increase with PRECAUTIONS). rolac tromethamine is CONTRAINDICATED in the
- setting of coronary artery bypass graft (CABG) surgery (see CONTRAINDICATIONS and WARNINGS).
- (see CONTRAINDICATED in patients 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
- NISK OF BLEEDING Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemor-hagic diathesis, incomplete hemostasis and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).
- Retorolac tromethamine is CONTRAINDICATED as prophy-lactic analgesic before any major surgery. HYPERSENSITIVITY
- Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when admin-istering 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).
- nonsteroidal anti-inflammatory drugs (NSAIDS). INTRATHECAL OR EPIDURAL ADMINISTRATION Ketorolac tromethamine is CONTRAINDICATED for intra-thecal 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 inbihit uterine contractions
- circulation and inhibit uterine contractions.
- CONCOMITANT USE WITH NSAIDS
   Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving aspirin or NSAIDs because of the cumu-lative risk of inducing serious NSAID-related side effects.
- lative risk of inducing serious NSAID-related side effects. SPECIAL POPULATIONS Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs.) of body weight (see DOSAGE 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. DOSAGE AND ADMINISTRATION Ketorolac Tromethamine Tablets

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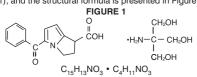
Ketorolac

**Tromethamine** 

Injection, USP Rx only

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

# DESCRIPTION Ketorolac Tromethamine Injection, USP is a member of the Nettodat inflation in the inflation (SP) is a finite field of the pyrrolo-pyrrole group of nonsteroidal anti- inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is $(\pm)$ -5-benzoyl-2,3- dihydro-1<u>H</u>-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1), and the structural formula is presented in Figure 1.



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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 pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 378 40

is 376.40. Ketorolac Tromethamine Injection, USP is available for intra-venous (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 avail-able for intramuscular administration only. The solutions contain 0.1% citric acid, 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 hydro-chloric acid. The sterile solutions are clear and slightly yellow in color.

### CLINICAL PHARMACOLOGY

Pharmacokinetic Parameters (units)

C<sub>max<sup>2</sup></sub> (mcg/mL) [Single-dose]

C<sub>max</sub> (mcq/mL) [steady state gid]

C<sub>min<sup>3</sup></sub> (mcg/mL) [steady state qid]

Cavo<sup>4</sup> (mcg/mL) [steady state qid]

Bioavailability (extent)

T<sub>max</sub><sup>1</sup> (min)

 $V_{\beta}^{5}$  (L/kg)

Pharmacodynamics (etorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models. The nechanism of action of ketorolac, like that of other NSAIDs, is not

Oral<sup>†</sup>

10 mg

 $44 \pm 34$ 

 $0.87 \pm 0.22$ 

 $1.05 \pm 0.26*$ 

0.29±0.07\*\*

 $0.59 \pm 0.2^{**}$ 

15 mg

33±21\*\*

1.14±0.32\*\*

 $1.56 \pm 0.44*$ 

0.47±0.13\*\*

0.94±0.29\*\*

completely understood but may be related to prostaglandin synthe-tase 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 Intravenous, Intramuscular and Oral

Pharmacokinetics The pharmacokinetics of ketorolac tromethamine, following intrave-nous, intramuscular, and oral doses of ketorolac tromethamine are compared in Table 1. In adults, the extent of bioavailability following administration of the oral and intramuscular forms of ketorolac tromethamine was equal to that following an intravenous bolus.

60 mg

33±21\*\*

4.55±1.27\*\*

N/A<sup>††</sup>

N/A

N/A

100%

Table 1: Table of Approximate Average Pharmacokinetic Parameters (Mean±SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Intravenous Bolus<sup>‡</sup>

15 mg 30 mg

1.1±0.7\*\* 2.9±1.8

 $0.210 \pm 0.044$ 

 $4.65 \pm 0.96$ 

 $6.85 \pm 2.61$ 

 $1.04 \pm 0.35$ 

 $2.17 \pm 0.59$ 

2.47±0.51\*\*

3.09±1.17\*\*

0.61±0.21\*\*

 $1.09 \pm 0.3 * *$ 

r and Oral mean age = 40, range Estimated from 30 mg single intramuscular doses of ketorolac tromethamine

INDICATIONS AND USAGE

CONTRAINDICATIONS

WARNINGS)

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).
Acute Pain in 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 intravenous or intramuscular dosing of ketorolac tromethamine, and oral ketorolac tromethamine is to be used only as continuation freatment, 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, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS). Patients should be switched to alternative analgesics as soon as possible.

should be switched to alternative analgesics as soon as poss but ketorolac tromethamine therapy is not to exceed 5 days.

(see also **Boxed WARNING**) (See also **Boxed WARNING**) Ketorolac Tromethamine is contraindicated in patients with previ-ously 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 a constrainted in patients.

bleeding or perforation and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Ketorolac tromethamine should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS – Anaphylactoid Reactions**, and **PRECAUTIONS** – **Pre-existing Asthma**). Ketorolac tromethamine is contraindicated as prophylactic analgesic before any major surgery. Ketorolac tromethamine is contraindicated 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 deliver

Ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine muscula-ture, thus increasing the risk of uterine hemorrhage. Ketorolac tromethamine inhibits platelet function and is, there-fore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).

and PHECAU IIONS). 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

<sup>3</sup> Liters/hour/kilogram Intravenous-Administration: In normal subjects (n=37), the total clearance of 30 mg intravenous-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 intravenous dosing of ketorolac tromethamine in pediatric patients.) CLINICAL STUDIES 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. Adult Patients In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine intrave-nous 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 post-dosing pain assessment times, in the patients receiving ketorolac tromethamine intravenous plus PCA morphine as compared to patients receiving PCA-administered morphine alone. Adult Patients

% Dose metabolized = <50 % Dose excreted in urine = 91 % Dose excreted in feces = 6% Plasma protein binding = 99

Derived from PO pharmacokinetic studies in 77 normal fasted volunteers

Derived from intramuscular pharmacokinetic studies in 54 normal volunteers Derived from intravenous pharmacokinetic studies in 54 normal volunteers

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

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

------ 0.175±0.039 -

ime-to-peak plasma concentration

Peak plasma concentration

- Trough plasma concentration
- <sup>4</sup> Average plasma concentration
   <sup>5</sup> Volume of distribution

### Linear Kinetics

Linear Kinetics In adults, following administration of single oral, intramuscular or intravenous 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 intramuscular, intravenous, or recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the corcentrations of free and bound recement in the concentrations of free and bound racemate.

### Distribution

**Distribution** The mean apparent volume  $(V_{B})$  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**) PRECAUTIONS – Nursing Mothers)

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, approxi-mately 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 S-enantiomer is cleared approximately two times faster than the S-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 after 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. The principal route of elimination of ketorolac and its metabolites

### Accumulation

Ketorolac tromethamine administered as an intravenous 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  $\pm$  0.13) on Day 1 and 0.55 mcg/mL (SD  $\pm$  0.23) on Day 6. Steady state was approached after the

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

Intramuscular\*

30 mg

44±29

 $2.42 \pm 0.68$ 

3.11±0.87\*\*

0.93±0.26\*\*

1.88±0.59\*\*

Based on single-dose data only, the half-life of the ketorolac based on single-dose data only, the name of the keloblac tromethamine racemate increased from 5 to 7 hours in the lederly (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  $\pm$  0.77; young, 2.99 mcg/mL  $\pm$  1.03) (see **PRECAUTIONS – Geriatric Use**).

Pediatric Patients Limited information is available regarding the pharmacokinetics of dosing of ketorolac tromethamine in the pediatric popula-tion. 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  $\pm$  1.6 hours, the average clearance was 0.042  $\pm$  0.01 L/hr/kg, the volume of distribution during the terminal phase (V<sub>B</sub>) was 0.34  $\pm$  0.12 L/kg and 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 intramuscular route in pediatric patients.

Renal Insufficiency Based on single-dose data only, the mean half-life of ketorolac

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>x</sub> of each enantiomer increased by approximately 100% compared with healthy volunceers. The volume of distribution doubles for the S-enantiomer and increase by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

unbound fraction. The AUC<sub>x</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,  $AUC_{\infty}$ and C<sub>max</sub>, in 7 patients with liver disease compared to healthy volunteers (see **PRECAUTIONS – Hepatic Effects** and **Table 2**).

Pharmacokinetic differences due to race have not been identified.

Nachallos can cause serious side effects, including: may happen early in treatment and may increases:
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NasAIDs after a recent heart attack if you as anytime during uncluster is obtaching, ulcers, and tears (perfortation) of the esophagus.
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is contraindicated.



Table 2: The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of nine (Intramuscular<sup>1</sup> and Oral<sup>2</sup>) in Adult Population

	Total Clearance [in L/h/kg] <sup>3</sup>		Terminal Half-life [in hours]	
Type of Subjects	Intramuscular Mean (range)	Oral Mean (range)	Intramuscular Mean (range)	Oral Mean (range)
Normal Subjects Intramuscular (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 Intramuscular (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 Intramuscular 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 Intramuscular (n = 25), Oral (n = 9) serum creatinine = 1.9-5.0 mg/dL, mean age (Intramuscular) = 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 Intramuscular and Oral ( $n = 9$ ) mean age = 40, range = 27-63	0.016 (0.003- 0.036)	-	13.6 (8.0-39.1)	-

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

WARNINGS (See also Boxed WARNING.) The total combined duration of use of oral ketorolac trometh-amine and intravenous or intramuscular dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac trometh-amine 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 natients who develop a serious upper GI The most serious risks associated with ketorolac tromethamine are:

with ketorolac tromethamine. Only one in five patients who develop a serious upper Gl adverse event on NSAID therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with ketorolac tromethamine. Do not use ketorolac tromethamine for more than five days. However, even short-term therapy is not without risk. In addi-tion to past history of ulcer disease. other factors that increase

However, even short-term therapy is not without risk. In addi-tion 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

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 care-fully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concur-rently; 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 thest diffects hemostasis of the provide the studies durable.

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 associa-tion with the peri-operative use of intravenous or intramuscular 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**).

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 prosta-glandin formation and, secondarily, in renal blood flow, which may precipitate over renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

by recovery to the pretreatment state. Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see **DOSAGE 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.

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 decom-pensation 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.

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.

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The development of such events, inrolgnout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associ-ated with NSAID use. The concurrent use of aspirin and an NSAID, such as ketorolac tromethamine, increases the risk of serious gastrointestinal (GI) events (see WARNINGS).

Status Post Coronary Artery Bypass Graft (CABG) Surgery Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG surgery (see CONTRAINDICATIONS).

(see CONTRAINDICATIONS). **Post-MI Patients** Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years follow-up. Avoid the use of ketorolac tromethamine in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ketorolac tromethamine is used in patients with a recent MI, monitor patients for signs of cardiac ischemia. **Hypertension** 

With a recent with individual patients for signs or our duce isometric. 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. Loost Esilure and Edema

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

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ketorolac tromethamine may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs) (see **PRECAUTIONS-Drug** 

Interactions). Avoid the use of ketorolac tromethamine in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ketorolac tromethamine is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

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

# Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ketorolac tromethamine. Some of these events have been fatal or life-threat-ening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ketorolac tromethamine and evaluate the patient immediately. Estal Toxicity

**Fetal Toxicity** <u>Premature Closure of Fetal Ductus Arteriosus:</u> Avoid use of NSAIDs, including ketorolac tromethamine, in pregnant women at about 30 weeks gestation and later. NSAIDs including ketorolac tromethamine, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

the fetal ductus arteriosus at approximately this gestational age. Oligohydramnios/Neonatal Renal Impairment: Use of NSAIDs, including ketorolac tromethamine, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ketorolac tromethamine use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ketorolac tromethamine treatment extends beyond 48 hours. Discontinue ketorolac tromethamine if oligohydramnios ccurs and follow up according to clinical practice (see **PRECAUTIONS; Pregnancy**).

oligohydramnios occurs and follow u (see **PRECAUTIONS; Pregnancy**). PRECAUTIONS

### General

Ketorolac tromethamine cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinu-ation of corticosteroids may lead to disease exacerbation. Patients ation of conticosteroids 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.

conditions.

### Hepatic Effects

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.

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 Gl 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 dura-tion, 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. Pra-evisting Asthma

Pre-existing Asthma Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin- sensitive asthma has been associate

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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 ketor-olac tromethamine treatment (see Boxed WARNING, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections), instruct intervent to each endload educe if their develop tetrations.

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 family members and to discard any unused drug. Remember that the total combined duration of use of oral ketorolac tromethamine and intravenous or intramuscular dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients. Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Advise patients to be alert for the symptoms of cardiovascular 1. Advise patients to be aler for the Symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weak-ness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately (see WARNINGS).
2. Ketorolac tromethamine, like other NSAIDs, can cause GI

discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and he emesis ould be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal Effects: Risk of Ulceration Bleeding, and Perforation). 3. Serious Skin Reactions, including DRESS

Bleeding, and Perforation).
 3. Serious Skin Reactions, including DRESS
 Advise patients to stop taking ketorolac tromethamine immediately if they develop any type of rash or fever and to contact their healthcare provider as scon as possible (see WARNINGS).
 4. Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur (see WARNINGS).
 5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms.
 6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).
 7. Fetal Toxicity
 Inform pregnant women to avoid use of ketorolac tromethamine and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with ketorolac tromethamine is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours (see WARNINGS; Fetal Toxicity, PRECAUTIONS; Pregnancy).

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

Drug Interactions Ketorolac is highly bound to human plasma protein (mean 99.2%). There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

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

In a study involving 12 adult volunteers, oral ketorolac trometh-amine was coadministered with a single dose of 25 mg warfaring In a study involving 12 adult volunteers, oral ketorolac trometh-amine was coadministered with a single dose of 25 mg warfarin, causing no significant changes in pharmacokinetics or pharma-codynamics of warfarin. In another study, ketorolac tromethamine dosed intravenous or intramuscular was given with two doses of 5000 U of heparin to 11 healthy volunteers, resulting in a mean template bleeding time of 6 minutes (3.2 to 11.4 min) compared to a mean of 6.0 minutes (3.4 to 7.5 min) for heparin alone and 5 1 minute (25 to 6 5 min) for heparin alone and 5 1 minute (25 to 6 5 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac trometh amine and warfarin or heparin, the administration of ketorola tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitore. (see WARNINGS and PRECAUTIONS – Hematologic Effects).

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

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

### Diuretics

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

### Probenecid

Concomitant administration of oral ketorolac tromethamine and Concomitant administration of oral ketorolac tromethamine and probenecid resulted in decreased clearance and volume of distri-bution of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately threefold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately twofold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

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

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

# ACE Inhibitors/Angiotensin II Receptor Antagonists Concomitant use of ACE inhibitors and/or angiotensin II receptor antagonists may increase the risk of renal impairment, particularly in volume-depleted patients.

Reports suggest that NSAIDs may diminish the antihypertensive affect of ACE inhibitors and/or antiotensin II records effect of ACE inhibitors and/or angiotensin II receptor antagonists. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors and/or angiotensin II receptor antagonists.

### Antiepileptic Drugs

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

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

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

Nondepolarizing Muscle Relaxants In postmarketing experience there have been reports of a possible interaction between ketorolac tromethamine intravenous/intra-muscular and nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Selective Serotonin Reuptake Inhibitors (SSRIs) There is an increased risk of gastrointestinal bleeding when selec-tive serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administered concomitantly with SSRIs.

## Carcinogenesis, Mutagenesis, and Impairment of Fertility An 18-month study in mice with oral doses of ketorolac trometh-

amine tablets at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended intramuscular or intravenous dose f 30 mg gid, based on area-under-the-plasma-concentration curve

of 30 mg qlq, based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity. Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward muta-tion assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells. ovarian cells

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

### Pregnancy

Pregnancy Risk Summary Use of NSAIDs, including ketorolac tromethamine, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of ketorolac tromethamine use between about 20 and 30 weeks of gestation, and avoid ketorolac tromethamine use at about 30 weeks of gestation and later in pregnancy (see WARN-INGS; Fetal Toxicity).

### Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including ketorolac tromethamine, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

### Oligohvdramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairmer

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. Reproduction studies have been performed during organogenesis using daily oral doses

of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. However, animal reproduction studies are not always predictive of human response. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation Day 17, caused dystocia and higher pup mortality in rats. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ketorolac, resulted in increased pre- and post-implantation loss. Prostaglandin synthesis inhibitors have been reported to impair kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## Clinical Considerations Fetal/Neonatal Adverse Reactions

## Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including ketorolac trometh-amine, can cause premature closure of the fetal ductus arteriosus (see WARNINGS; Fetal Toxicity).

Oligohydramnios/Neonatal Renal Impairment: If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If ketorolac tromethamine treatment extends beyond 48 hours, consider monitoring with ultrasound for oligo-hydramnios. If oligohydramnios occurs, discontinue ketorolac tromethamine and follow up according to clinical practice (see WARNINGS; Fetal Toxicity).

### n Data

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

Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

### os/Neonatal Renal Impairment:

Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis. Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generaliz-ability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain. Labor and Deliverv

### Labor and Delivery

The use of ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage (see CONTRAINDICATIONS).

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

Nursing Mothers Limited data from one published study that included 10 breast-feeding women 2-6 days postpartum showed low levels of ketorolac in breast milk and were undetectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 mg of ketorolac tromethamine, the maximum milk-to-plasma ratio was 0.037. After 1 day of dosing (10 mg every 6 hours), the maximum milk concentration was 7.9 ng/mL, and the maximum milk-to-plasma ratio was 0.025. Assuming a daily intake of 400-1,000 mL of human milk per day and a maternal body weight of 60 kg, the calculated maximum daily infant exposure was 0.00263 mg/kg/day, which is 0.4% of the maternal weight-adjusted dose.

0.4% of the maternal weight-adjusted dose. Exercise caution when ketorolac is administered to a nursing woman. Available information has not shown any specific adverse events in nursing infants; however, instruct patients to contact their infant's healthcare provider if they note any adverse events.

### Pediatric Use

Ketorolac tromethamine is not indicated for use in pediatric patients. The safety and effectiveness of ketorolac tromethamine in pediatric patients below the age of 17 have not been established.

Geriatric Use (≥65 Years of Age)

Because ketorolac tromethamine may be cleared more slowly by the elderly (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 DOSAGE AND ADMINISTRATION) and careful clinical monitoring must be used when treating the elderly with ketorolac tromethamine.

### ADVERSE REACTIONS

### To report SUSPECTED ADVERSE REACTIONS, contact Free Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088

or www.fda.gov/medwatch. 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, anaph naphylactic and anaphylactoid reactions and ad WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION). These NSAID-related plications can be serious in certain patients for whom ketorola romethamine is indicated, especially when the drug is used

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:

astrointestinal (GI) experiences including:			
dominal pain	constipation/ diarrhea	dyspepsia	
tulence	GI fullness	Gl ulcers (gastric/duodenal)	
oss bleeding/ rforation	heartburn	nausea*	
omatitis	vomiting		
her experiences:			
normal renal nction	anemia	dizziness	
owsiness	edema	elevated liver enzymes	
adaches*	hypertension	increased bleeding time	

injection site pain pruritus purpura rashes tinnitus sweating

\* Incidence greater than 10%

Additional adverse experiences reported occasionally (<1% in atients taking ketorolac tromethamine or other NSAIDs in clinical

Body as a Whole: fever, infections, sepsis Cardiovascular: congestive heart failure ascular: congestive heart failure, palpitation, pallor,

Cardiovascular: congestive neart failure, palpitation, palior, tachycardia, syncope Dermatologic: alopecia, photosensitivity, urticaria Gastrointestinal: anorexia, dry mouth, eructation, esopha-gitis, 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, abn

anxiety, asthenia, confusion, depression, euphoria, extrapyramidal symptoms, hallucinations, hyperkinesis, inability to concentrate, omnia, nervousness, paresthesia, somnolence, stupor, tremors /ertigo, malaise

igo, inalaise eproductive, female: infertility espiratory: asthma, cough, dyspnea, pulmonary edema,

pecial Senses: abnormal taste, abnormal vision, blurred vision,

equency, interstitial nephritis, oliguria/polyuria, increased urinary requency, interstitial nephritis, oliguria/polyuria, proteinuria, renal ailure, urinary retention Other rarely observed reactions (reported from postmarketing experience in patients taking ketorolac tromethamine or other NSAIDs) 2

NSAIDs) are: **Body as a Whole:** angioedema, death, hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, iongue edema (see **WARNINGS**), myalgia **Cardiovascular:** arrhythmia, bradycardia, chest pain, flushing, nypotension, myocardial infarction, vasculitis **Dermatologic:** exfoliative dermatitis, erythema multiforme, Lyell's syndrome, bullous reactions including Stevens-Johnson syndrome and toxic enidermal nercolvsis

d toxic epidermal necrolvsis

Ind toxic epidermal necrolysis Gastrointestinal: acute pancreatitis, liver failure, ulcerative tomatitis, exacerbation of inflammatory bowel disease (ulcerative olitis. Crohn's disease) Hemic and Lymphatic: agranulocytosis, aplastic anemia, hemo-

lytic 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,

hemolytic uremic syndrome

Postmarketing Surveillance Study

ycnosis **Respiratory:** bronchospasm, respiratory depression, pneumonia **Special Senses:** conjunctivitis **Urogenital:** flank pain with or without hematuria and/or azotemia, used the sense of the se

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

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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

A. Adult Patients without History of PUB

of age

of age

≥65 years

OVERDOSAGE

Age of	Total Daily Dose of Ketorolac Tromethamine Injection			
Patients	≤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				

### Total Daily Dose of Ketorolac Tromethamine Injection

≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
2.1%	4.6%	7.8%	15.4%
4.7%	3.7%	2.8%	25.0%

## Symptoms and Signs Symptoms following act

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 depresented and acute acute and 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.

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 hemoperfu-sion 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. DOSAGE AND ADMINISTRATION

DOSAGE 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 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 intravenous or intramuscular dosing of ketorolac tromethamine and oral ketorolac tromethamine is not to exceed 5 days. In adults, the use of oral ketorolac tromethamine is only indi-cated as continuation therapy to intravenous or intramuscular dosing of ketorolac tromethamine. See package insert for ketorolac tromethamine tablets for transition from intravenous or intramuscular dosing of 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 intravenous or intramuscular 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 trometh-amine therapy is not to exceed 5 days. When administering ketorolac tromethamine injection, the intra-venous bolus must be given over no less than 15 seconds. The intramular administerior bould be sized advect and dooply intramuscular 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 intravenous or intramuscular. Duration of analgesic effect is usually 4 to 6 hours.

Single-Dose Treatment: The following regimen should be limited to single administration use only Intramuscular Dosing
Patients <65 years of age: One dose of 60 mg.</li>
Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One dose of 30 mg.

Intravenous 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.

50 kg (110 lbs) of body weight: One dose of 15 mg.
Multiple-Dose Treatment (Intravenous or Intramuscular)
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.</li>
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.

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Other information about N:
Aspirin is an NSAID me does not increase the cha attack. Aspirin can cause brain, stomach, and intescan also cause ulcers in and intestines.
Some NSAIDs are sold in without a prescription (over Talk to your healthcare prusing over-the-counter NS than 10 days.
General information about effective use of NSAIDs
Medicines are sometimes proposes other than those lis cation Guide. Do not use I condition for which it was me they have the same sympthave. It may harm them. sAID m se the ch an cause , and int ulcers , me , chan use b<sup>l</sup> intes ers in **NSAI** nedic bleed sstine n the din e to PG a but hea in th spiri

Pharmaceutical Information for Ketorolac Tromethaming

Injection Ketorolac tromethamine injection should not be mixed in a small volume (e.g., in a syringe) with morphine sulfate, meperidine Volume (e.g., If a symge) with morphine subate, meperiome hydrochloride, promethazine hydrochloride or hydroxyzine hydro-chloride; 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 FOR INTRAMUSCULAR OR INTRAVENOUS LISE

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Product Code	Unit of Sale	Strength	Each
60101	NDC 63323-161-01 Unit of 25	15 mg per mL	NDC 63323-161-00 1 mL fill in a 2 mL single dose vial
RF160201	NDC 63323-162-51 Unit of 25	30 mg per mL	NDC 63323-162-11 1 mL fill in a 2 mL single dose vial This product contains an RFID.
60201	NDC 63323-162-01 Unit of 25	30 mg per mL	NDC 63323-162-00 1 mL fill in a 2 mL single dose vial

FOR INTRAMUSCULAR USE ONLY. NOT FOR INTRAVENOUS

Product Code	Unit of Sale	Strength	Each
160202	NDC 63323-162-02	60 mg per 2 mL	NDC 63323-162-03
	Unit of 25	(30 mg per mL)	2 mL single dose vial

The container closure is not made with natural rubber latex. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room mperature.

Protect from light

Retain in carton until time of use

FRESENIUS KABI Lake Zurich, IL 60047 www.fresenius-kabi.com/us

Revised: April 2024

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