

### Ketorolac Tromethamine Injection, USF FOR INTRAVENOUS/INTRAMUSCULAR USE (15 mg and 30 mg)

FOR INTRAMUSCULAR USE ONLY (60 mg)

Rx only

WARNING Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days in adults) management of noderately severe acute pain that requires analgesia at the opioid level. Oral ketorolac tromethamine is indicated only as continua following intravenous or intramuscular dosing of ketorolac tromethamine, if necessary. The total combined duration of use of oral ketorolac tion 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 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 ntestinal bleeding. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

 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 PRECAUTIONS).

nine is CONTRAINDICATED in the setting of coronary artery bypass graft (CABG) surgery (see CONTRAINDICATIONS and 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).

• Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed

### cular 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

### oidal anti-inflammatory drugs (NSAIDs) INTRATHECAL OR EPIDURAL ADMINISTRATION

nethamine is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol conte

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

## **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.

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** 

- 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
- . The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine tablets.

injection (maximum 120 mg) (see DOSAGE AND ADMINISTRATION).

 $Ketorolac\ Tromethamine\ Injection, USP\ is\ a\ member\ of\ the\ pyrrolo-pyrrole\ group\ of\ nonsteroidal\ anti-inflammatory\ drugs\ (NSAIDs).\ The\ chemical\ name\ for\ pyrrolo-py$ ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid compound with 2-Amino-2-(hydroxymethyl)-1,3-propanediol (1:1) and the structural formula is presented in Figure 1.

 $Ketorolac\ tromethamine\ is\ a\ racemic\ mixture\ of\ [\cdot] S\ and\ [+] R\ ketorolac\ tromethamine.\ Ketorolac\ tromethamine\ may\ exist\ in\ three\ crystal\ forms.\ Freely$ soluble in water and in methanol: slightly soluble in alcohol, in dehydrated alcohol, and in tetrahydrofuran: practically insoluble in acetone, in dichloromethane, in toluene, in ethyl acetate, in dioxane, in hexane, in butyl alcohol, and in acetonitrile. Ketorolac tromethamine has a pKa of 3.5 and an noctanol/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 intramuscular ad contain 10% (w/v) alcohol, USP, 1 mg. 1 mg and 2 mg, respectively of citric acid anhydroxiae 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 hydroxide acid. The sterile solutions are clear and

## CLINICAL PHARMACOLOGY

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 synthetase inhibition. The biological activity of ketorolac tromethamine is associated with the S-form.

## Ketorolac tromethamine possesses no sedative or anxiolytic properties

The peak an algesic effect of ketorolac trome tham in e occurs within 2 to 3 hours and is not statistically significantly different over the recommended do sage and the peak and the pearange of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route is in the duration of

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

In adults, the extent of bigavailability following administration of the oral and intramuscular forms of ketorolac tromethamine was equal to that following an

 $Table \ 1: Table \ of \ Approximate \ Average \ Pharmacokinetic \ Parameters \ (Mean \pm SD) \ Following \ Oral, \ Intramuscular \ and \ Intravenous \ Doses \ of \ Pharmacokinetic \ Parameters \ (Mean \pm SD) \ Following \ Oral, \ Intramuscular \ and \ Intravenous \ Doses \ of \ Pharmacokinetic \ Parameters \ (Mean \pm SD) \ Following \ Oral, \ Intramuscular \ and \ Intravenous \ Doses \ of \ Pharmacokinetic \ Parameters \ (Mean \pm SD) \ Following \ Oral, \ Intramuscular \ and \ Intravenous \ Doses \ of \ Pharmacokinetic \ Parameters \ (Mean \pm SD) \ Following \ Oral, \ Intramuscular \ And \ Intravenous \ Doses \ of \ Pharmacokinetic \ Pharmacokinetic \ Parameters \ (Mean \pm SD) \ Following \ Oral, \ Intramuscular \ And \ Pharmacokinetic \ Pharmac$ 

	Oral <sup>†</sup>		Intramuscular*		Intravenous I	Bolus <sup>‡</sup>
Pharmacokinetic Parameters (units)	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T <sub>max</sub> (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 qid]	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> (mcg/mL) [steady state qid]	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> (mcg/mL) [steady state qid]	0.59±0.2**	0.94±0.29**	1.88±0.59**	N/A	1.09±0.3**	2.17±0.59
V <sub>β</sub> <sup>5</sup> (L/kg)	0.175±0.039			0.210±0.044		
ν <sub>β</sub> (L/kg/				Time to neak plas		

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

\* Derived from oral pharmacokinetic studies in 77 normal fasted volunteers Derived from intramuscular pharmacokinetic studies in 54 normal volunteer

\* Derived from intravenous pharmacokinetic studies in 24 normal volunteers 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 C,,, and T,,,data

% Plasma protein binding = 99

### **Linear Kinetics** In adults, following administration of single oral, intramuscular or intravenous doses of ketorolac tromethamine in the recommended dosage ranges, the

% Dose excreted in urine = 91

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 proportiona increase in the concentrations of free and bound racemate. Distribution

The mean apparent volume (V<sub>p</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  $high as 10\,mcg/mL\,will\,only\,occupy\,approximately\,5\%\,of\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,unbound\,fraction\,for\,each\,enantiomer\,will\,be\,constant\,over\,the\,albumin\,binding\,sites.\,Thus,\,the\,albumin\,binding\,sites,\,the\,albumin\,binding\,s$ therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations  $Ketorolac\ tromethamine\ is\ excreted\ in\ human\ milk\ (see\ \textbf{PRECAUTIONS}-\textbf{Nursing}\ \textbf{Mothers}).$ 

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

Table 2 (see CLINICAL PHARMACOLOGY - Kinetics in Special Populations).

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  $10\,\mathrm{mg}$  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 after each dose. There is little or no inversion of the Rns. The clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined in

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD  $\pm$  0.4) compared with 5 hours (SD  $\pm$  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 are studies. Accumulation

Ketorolac tromethamine administered as an intravenous bolus, every 6 hours, for 5 days, to healthy subjects (n = 13), showed no significant difference in  $C_{max}$  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

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  $C_{\text{max}}$  for the two groups (elderly, 2.52 mcg/mL  $\pm$  0.77; young,  $2.99 \, \text{mcg/mL} \pm 1.03$ ) (see PRECAUTIONS – Geriatric Use). **Pediatric Patients** 

## Limited information is available regarding the pharmacokinetics of dosing of ketorolac tromethamine in the pediatric population. Following a single intravenous bolus dose of $0.5\,\mathrm{mg/kg}$ in $10\,\mathrm{children}\,4$ to $8\,\mathrm{years}\,$ old, the half-life was $5.8\,\pm\,1.6$ hours, the average clearance was $0.042\,\pm\,0.01\,\mathrm{L/hr/kg}$ , the

volume of distribution during the terminal phase ( $V_o$ ) was  $0.34 \pm 0.12$  L/kg and the volume of distribution at steady state ( $V_o$ ) was  $0.26 \pm 0.08$  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 intramuscular 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  $AUC_{\infty}$  of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by  $1/5^{\circ}$  for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

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 $C_{\max}$ , 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

 $Table\ 2: The\ Influence\ of\ Age,\ Liver\ and\ Kidney\ Function,\ on\ the\ Clearance\ and\ Terminal\ Half-life\ of\ Ketorolac\ Tromethamine\ (Intramuscular transcellar tra$ and Oral2) in Adult Populations

	Total Clearance [in L/h/kg]³		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 to 60 Oral (n = 77) mean age = 32, range = 20 to 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 to 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 to 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)

		learance  h/kg]³	Terminal Half-life [in hours]	
Type of Subjects	Intramuscular Mean (range)	Oral Mean (range)	Intramuscular Mean (range)	Oral Mean (range)
Patients with Renal Impairment Intramuscular (n = 25), Oral (n = 9) serum creatinine = 1.9·5.0 mg/dL, mean age (Intramuscular) = 54,				
range = 35 to 71 mean age (Oral) = 57, range = 39 to 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 to 63	0.016 (0.003-0.036)	_	13.6 (8.0-39.1)	_

<sup>3</sup> Liters/hour/kilogram

In normal subjects (n = 37), the total clearance of 30 mg intravenous-administered ketorolac tromethamine was 0.030 (0.017 to 0.051) L/h/kg. The terminal half-life was 5.6 (4.0 to 7.9) hours. (see **Kinetics in Special Populations** for use of intravenous dosing of ketorola CLINICAL STUDIES

## Adult Patients In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine intravenous as fixed

intermittent boluses (e.g., 30 mg initial dose followed by 15 mg every 3 hours), 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 intravenous plus PCA morphine 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). Acute Pain in Adult Patients olac tromethamine is indicated for the short-term (  $\leq$  5 days) management of moderately severe acute pain that requires analgesia at the opioid leve 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 treatment, 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, but

### CONTRAINDICATIONS (see also Boxed WARNING)

Ketorolac tromethamine is contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation and

in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Ketorolac tromethamine should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (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 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-

The concomitant use of ketorolac tromethamine and probenecid is contraindicated

The concomitant use of ketorolac tromethamine and pentoxifylline is contraindical Ketorolac tromethamine injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol conten

## WARNINGS

(see also Boxed WARNING)
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. . most serious risks associated with ketorolac trometha

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 ketorola

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with ketorolac tromethamine. Do not use ketorolac tromethamine for more than 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, specia care should be taken in treating this population.

To minimize the notential 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 evaluations of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluations of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluations. 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

Because prostaglanding play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients because prostagiantian play an implication in the minimastas and incharacteristic prostagiantial programs are according to the management who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and therapy that affects hemostasis, including prophylactic low-dose heparin (2500 to 5000 units every 12 hours), warfarin and dextrans have not been studie 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

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association 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).

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 Long-term administration to resorted in a resorted in terms papinary recross and under lentangury, retend toxicity has asso used seen in patients in wind remail 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 a greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (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 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 sation or failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients. As with other NSAIDs, anaphylactoid reactions may occur in natients 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 occu

## 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) ding myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incid of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first few weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of pr symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The

concurrent use of aspirin and an NSAID, such as ketorolac tromethamine, increases the risk of serious gastrointestinal (GI) events (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 ncidence of myocardial infarction and stroke. NSAIDs are traindicated in the setting of CABG surgery (see CONTRAINDICATIO

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

VSAIDs, 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

events. If ketorolac tromethamine is used in patients with a recent MI, monitor patients for signs of cardiac ischemia

closely during the initiation of NSAID treatment and throughout the course of therapy. **Heart Failure and Edema** The Coxih and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a

Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death, Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ketorolac tromethamine may blunt the CV effects several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs) (se

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

Serious 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. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as neralized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of ketorolac tromethamine injection at the first appearance of skin rash or any other sign of hypersensitivity. Ketorolac tromethamine injection is contraindicated in patients with previous serious skin reactions to NSAIDs (see

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-threatening. 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

### **Fetal Toxicity** Premature Closure of Fetal Ductus Arteriosus:

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Avoid use of NSAIDs, including ketorolac tromethamine, in pregnant women at about 30 weeks gestation and later, NSAIDs including ketorolac ethamine, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age Olinohydramnios/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 occurs and follow up according to clinical practice (see PRECAUTIONS; Pregnancy). PRECAUTIONS 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

The pharmacological activity of ketorolac tromethamine in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications

made to discontinue corticosteroids.

Ketorolac tromethamine should be used with caution in patients with impaired benatic 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

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

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

## NSAIDs can cause serious side effects, including:

- Increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase:
- with increasing doses of NSAIDs
- with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

• Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:

anvtime during use

 without warning symptoms that may cause death

The risk of getting an ulcer or bleeding increases with:

 increasing doses of NSAIDs past history of stomach ulcers, or stomach or intestinal longer use of NSAIDs bleeding with the use of NSAIDs smoking • taking medicines called drinking alcohol "corticosteroids", older age

> advanced liver disease bleeding problems

poor health

## NSAIDs should only be used:

"SSRIs", or "SNRIs"

"anticoagulants",

exactly as prescribed

at the lowest dose possible for your treatment

· for the shortest time needed

## What are NSAIDs? NSAIDs 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.

Do not take NSAIDs:

Who should not take NSAIDs?

 right before or after heart bypass surgery. Before taking NSAIDs, tell your healthcare provider about all of your medical

• if you had an asthma attack, hives, or other allergic reaction with aspirin or any

- conditions, including if you:
- have liver or kidney problems have high blood pressure
- · have asthma • are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for

healthcare provider may need to monitor the amount of fluid in your womb around your baby. You should not take NSAIDs after about 30 weeks of pregnancy. are breastfeeding or plan to breast feed Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements.

NSAIDs and some other medicines can interact with each other and cause serious side

more than 2 days when you are between 20 and 30 weeks of pregnancy, your

effects. Do not start taking any new medicine without talking to your healthcare

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including: See "What is the most important information I should know about medicines

- called NonSteroidal Anti-inflammatory Drugs (NSAIDs)?"
- new or worse high blood pressure
- heart failure
- liver problems including liver failure kidney problems including kidney failure
- low red blood cells (anemia) • life-threatening skin reactions
- life-threatening allergic reactions • Other side effects of NSAIDs include: stomach pain, constipation, diarrhea,

## gas, heartburn, nausea, vomiting, and dizziness. Get emergency help right away if you get 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 taking your NSAID and call your healthcare provider right away if you get
- nausea more tired or weaker than usual

itching

help right away.

diarrhea

written for health professionals.

any of the following symptoms:

- it is black and sticky like tar unusual weight gain
- skin rash or blisters with fever · your skin or eyes look yellow swelling of the arms and legs, hands and

vomit blood

 indigestion or stomach pain flu-like symptoms If you take too much of your NSAID, call your healthcare provider or get medical

• there is blood in your bowel movement or

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to

FDA at 1-800-FDA-1088.

## Other information about 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 NSAIDs 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

Medicines are sometimes prescribed for purposes other than those listed in a Medication

If you would like more information about NSAIDs, talk with your healthcare provider. You

can ask your pharmacist or healthcare provider for information about NSAIDs that is

## Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm

General information about the safe and effective use of NSAIDs

For more information, call 1-866-495-1995. This Medication Guide has been approved by the U.S. Food and Drug Administration.



## Medication Guide available at http://camberpharma.com/medicationguides

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iaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

 $A patient with symptoms and {\it lor signs suggesting liver} \ dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the$ 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 shoul

### 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 nemand a sometimes seeming promote receiving in control, including exercised collections. In the promote the promo 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 levelop 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.

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately (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 hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation).

Serious Skin Reactions, including DRESS  $Advise\ patients\ to\ stop\ taking\ ketorolac\ tromethamine\ immediately\ if\ they\ develop\ any\ type\ of\ rash\ or\ fever\ and\ to\ contact\ their\ health care\ provider$ 

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).

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy

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).

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 gattion, 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).

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

**Drug Interactions** orolac is highly bound to human plasma protein (mean 99.2%). There is no evidence in animal or human studies that ketorolac tromethamine induces or

## 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 two-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter ketorolac tromethamine protein binding.

In a study involving 12 adult volunteers, oral ketorolac tromethamine was coadministered with a single dose of 25 mg warfarin, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine doesd 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 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored (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

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

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 natient should be observed closely for signs of renal failure (see WARNINGS - Renal Effects), as well as to assure digretic efficacy.

Concomitant administration of oral ketorolac tromethamine and probenecid resulted in decreased clearance and volume of distribution of ketorolac and

significant increases in ketorolac plasma levels (total AUC increased approximately three-fold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increapproximately two-fold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity

oxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with meth

Concomitant use of ACE inhibitors and/or angiotensin II receptor antagonists may increase the risk of renal impairment, particularly in volume

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the

Reports suggest that NSAIDs may diminish the antihypertensive 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. Antienilentic 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 ket groups tromethamine is administered concurrently with nentoxifylline, 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/intramuscular and nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally

Selective Serotonin Reuptake Inhibitors (SSRIs) There is an increased risk of gastrointestinal bleeding when selective 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 tromethamine tablets at 2 mg/kg/day (0.9 times the human systemic exposure at the recomme

intramuscular or intravenous dose of 30 mg qid, 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 mutation assays. Ketorolac

recorded trongerment was not integer to me a mass test, mass a mass a mass and repair, and in lower missas and stronger and in toward missas and repair, and in lower missas and repair missas and r

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

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 be about 20 and 30 weeks of gestation, and avoid ketorolac tromethamine use at about 30 weeks of gestation and later in pregnancy (see WARNINGS; Fetal

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. Olianhydramnios/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

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 rabbits and at 10 mg/kg (1.0 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 tromethamine, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal 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 The saminate background risk of implications and installing of the latest population (s) summoves. An prepiator latest acceptance in the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

### **Clinical Considerations** Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arterios

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 tromethamine, 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 oligohydramnios. If oligohydramnios occurs, discontinue ketorolac tromethamine and follow up according to clinical practice (see WARNINGS; Fetal Toxicity)

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

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 invaprocedures, 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 generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain. **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 investigation of infertility, withdrawal of

### **Nursing Mothers** Limited data from one published study that included 10 breastfeeding women 2-6 days postpartum showed low levels of ketorolac in breast milk and were Limited user from the published survey that included in a Dreast teering worker 2-5 days posspartum showed row levels in the Religion and we will be undertectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 ng of ketorolac tromethamine, the maximum milk concentration observed was 7.3 ng/mL, and 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. 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 even

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 years have not been established

Geriatric Use (≥ 65 Years of Age)

Because ketorioac 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 ketorolad

## 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 tions 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 incl	uding:	
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, thrombocytopeniaMetabolic and Nutritional: weight change

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

Respiratory: asthma, cough, dyspnea, pulmonary edema, rhinitis Special Senses: abnormal taste, abnormal vision, blurred vision, hearing loss

Urogenital: cystitis, dysuria, hematuria, increased urinary frequency, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure, urinary reten 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, anaphylaxtoid 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 epider

necrolysis, and fixed drug eruption (FDE)  $\textbf{Gastrointestinal:} \ acute pancreatitis, liver failure, ulcerative stomatitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease)$ 

Hemic and Lymphatic: agranulocytosis, aplastic anemia, hemolytic anemia, lymphadenopathy, pancytopenia, post operative wound he

blood transfusion — see Boxed WARNING, WARNINGS, and PRECAUTIONS)  $\textbf{Metabolic and Nutritional:} \ \textbf{hyperglycemia, hyperkalemia, hyponat}$ 

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 and the syn

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 Ketorola	ac Tromethamine Injection		
A. Adult Patients withou	t History of PUB			
	Total Daily Dose of Ketorolac Tromethamine Injection			
Age of 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 H	istory of PUB			
	Total Daily Dose of Ketorolac Tromethamine Injection			
Age of Patients	≤ 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**

DOSAGE AND ADMINISTRATION

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.

Patients should be managed by symptomatic and supportive care following a NSAIDs overdose. There are no specific antidotes. 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.

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 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 indicated 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 (single- or multiple-dose) to multiple-dose oral ketorolac tromethamine.

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 "as needed" 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 intravenous bolus must be given over no less than 15 seconds. The intramuscular administration when a unimistering feet to the containing injection, the intravenous does made up went over no less trial 13 sections. The intramiss administration should be given solwly 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, 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.</li> Patients  $\geq$  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 (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.

For patients  $\geq$  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 "as needed" 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 solutio NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and

HOW SUPPLIED

Ketorolac tromethamine injection, USP is a sterile, clear and slightly yellow color solution and is supplied as follows:

Total Strength/Total Volume

Unit of Sale	(Concentration)
NDC 31722-305-10 Tray of 10 1 mL fill in a 2 mL single-dose glass fliptop vial NDC 31722-305-25 Tray of 25 1 mL fill in a 2 mL single-dose glass fliptop vial	15 mg/mL
NDC 31722-306-10 Tray of 10 1 mL fill in a 2 mL single-dose glass fliptop vial NDC 31722-306-25 Tray of 25 1 mL fill in a 2 mL single-dose glass fliptop vial	30 mg/mL
NDC* 31722-307-10 Tray of 10 2 mL fill in a 2 mL single-dose glass fliptop vial NDC* 31722-307-25 Tray of 25 2 mL fill in a 2 mL single-dose glass fliptop vial	60 mg/2 mL (30 mg/mL)

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

CAMBER Manufactured for:

Protect from light.

Camber Pharmaceuticals, Inc. Piscataway, NJ 08854

**∧** Aspiro Aspiro Pharma Limited . rvey No. 321, Biotech Park, Phase – III Karkapatla Village, Markook (Mandal)

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