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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 ketorolac tromethamine and ketorolac tromethamine injection should not exceed 5 days.

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

Gastrointestinal Risk

Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Therefore, ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

Cardiovascular 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 **PRECAUTIONS**).

Ketorolac Tromethamine Injection, USP, 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**).

Risk of Bleeding

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

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

Hypersensitivity

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

Intrathecal or Epidural Administration

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

Risk During Labor and Delivery

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

Concomitant Use with NSAIDs

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

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.

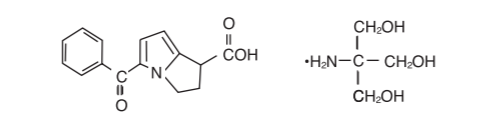
DOSAGE AND ADMINISTRATION

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 adverse events. The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine injection (maximum 120 mg) (see **DOSAGE AND ADMINISTRATION**).

DESCRIPTION

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



C₂₀H₂₄N₂O₆ **M.W. 376.41**

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.

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 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 is adjusted with sodium hydroxide and/or hydrochloric acid. The sterile solutions are clear and slightly yellow in color.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models.

The mechanism of action of ketorolac, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthesis inhibition. The analgesic 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 intravenous, 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.

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 concentrations of free and bound racemate.

Distribution

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

Ketorolac tromethamine is excreted in human milk (see **PRECAUTIONS, Nursing Mothers**).

Metabolism

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

Excretion

The principal route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg ketorolac tromethamine (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the

clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time 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.

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±0.13) on Day 1 and 0.55 mcg/mL (SD±0.23) on Day 6. Steady state was approached after the fourth dose.

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

Table 1: Table of Approximate Average Pharmacokinetic Parameters (Mean±SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine						
	Oral ¹		Intramuscular [*]		Intravenous Bolus [‡]	
Pharmacokinetic Parameters (units)	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T _{max} ¹ (min)	44±34	33±21**	44±29	33±21**	1.1±0.7**	2.9±1.8
C _{max} ² (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 _{max} (mcg/mL) [steady state qid]	1.05±0.26**	1.56±0.44**	3.11±0.87**	N/A ^{††}	3.09±1.17**	6.85±2.61
C _{min} ³ (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 _{min} ⁴ (mcg/mL) [steady state qid]	0.59±0.20**	0.94±0.29**	1.88±0.59**	N/A	1.09±0.30**	2.17±0.59
V _d ⁵ (L/kg)	0.175±0.039					
%Dose metabolized = <50	%Dose excreted in feces= 6					
%Dose excreted in urine= 91	%Plasma protein binding= 99					
¹ Derived from PO pharmacokinetic studies in 77 normal fasted volunteers						
² Derived from intramuscular pharmacokinetic studies in 54 normal volunteers						
³ Derived from intravenous pharmacokinetic studies in 24 normal volunteers						
⁴ Not applicable because 60 mg is only recommended as a single dose						
⁵ Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C _{max} and T _{max} data						
[†] Time-to-peak plasma concentration						
[‡] Peak plasma concentration						
⁴ Trough plasma concentration						
⁴ Average plasma concentration						
⁵ Volume of distribution						

Table 2: The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of Ketorolac Tromethamine (INTRAMUSCULAR ¹ and ORAL ²) in Adult Populations				
Type of Subjects	Total Clearance [in L/h/kg] ³		Terminal Half-life [in hours]	
	INTRAMUSCULAR Mean (range)	ORAL Mean (range)	INTRAMUSCULAR Mean (range)	ORAL Mean (range)
Normal Subjects	0.023 (0.010 to 0.046)	0.025 (0.013 to 0.050)	5.3 (3.5 to 9.2)	5.3 (2.4 to 9)
Intramuscular (n=54) mean age= 32, range= 18 to 60 Oral (n=77) mean age= 32, range= 20 to 60				
Healthy Elderly Subjects	0.019 (0.013 to 0.034)	0.024 (0.018 to 0.034)	7 (4.7 to 8.6)	6.1 (4.3 to 7.6)
Intramuscular (n=13), Oral (n=12) mean age= 72, range= 65 to 78				
Patients with Hepatic Dysfunction	0.029 (0.013 to 0.066)	0.033 (0.019 to 0.051)	5.4 (2.4 to 6.9)	4.5 (1.6 to 7.6)
Intramuscular and Oral (n=7) mean age= 51, range= 43 to 64				
Patients with Renal Impairment	0.015 (0.005 to 0.043)	0.016 (0.007 to 0.052)	10.3 (5.9 to 19.2)	10.8 (3.4 to 18.9)
Intramuscular (n=25), Oral (n=9) serum creatinine= 1.9 to 5 mg/dL, mean age (intramuscular)=54, range= 35 to 71 mean age (Oral)=57, range= 39 to 70				
Renal Dialysis Patients	0.016 (0.003 to 0.036)	-----	13.6 (8 to 39.1)	-----
Intramuscular and Oral (n=9) mean age= 40, range= 27 to 63				

¹Estimated from 30 mg single intramuscular doses of ketorolac tromethamine

²Estimated from 10 mg single oral doses of ketorolac tromethamine

³Liters/hour/kilogram

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_{0-∞} of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC_{0-∞} 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_{0-∞} and C_{max} in 7 patients with liver disease compared to healthy volunteers (see **PRECAUTIONS, Hepatic Effects and Table 2**).

Race

Pharmacokinetic differences due to race have not been identified.

Intravenous-Administration

In normal adult 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 to 7.9) hours (see **Kinetics in Special Populations** for use of intravenous dosing of ketorolac tromethamine in pediatric patients).

Clinical Studies

Adult Patients

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

INDICATIONS AND USAGE:

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

Acute Pain in Adult Patients

Ketorolac tromethamine is indicated for the short-term (maximum 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 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 the 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 ketorolac tromethamine therapy is not to exceed 5 days.

Ketorolac tromethamine injection has been used concomitantly with morphine and meperidine and has shown an opioid-sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the ketorolac tromethamine injection dosage range with low doses of narcotics prn, unless otherwise contraindicated. Ketorolac tromethamine injection and narcotics should not be

to outweigh the risk of recurrent CV thrombotic events. If Ketorolac Tromethamine Injection, USP is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Hypertension

NSAIDs, including ketorolac tromethamine, can lead to onset of new hypertension or worsening of 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.

Heart Failure and Edema

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

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

Avoid the use of Ketorolac Tromethamine Injection, USP, in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Ketorolac Tromethamine Injection, USP, 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.

Pregnancy

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

PRECAUTIONS:

General

Ketorolac tromethamine cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of ketorolac tromethamine in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

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

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketorolac tromethamine. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ketorolac tromethamine should be discontinued.

Hematologic Effects
Anemia is sometimes seen in patients receiving NSAIDs, including ketorolac tromethamine. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ketorolac tromethamine, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ketorolac tromethamine who may be adversely affected by alterations in platelet function,

such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-existing Asthma

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

Information for Patients

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

Physicians, when prescribing ketorolac tromethamine, should inform their patients or their guardians of the potential risks of ketorolac tromethamine treatment (see **Boxed WARNING, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS** sections), instruct patients to seek medical advice if they develop treatment-related adverse events, and advise patients not to give oral ketorolac tromethamine to other 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**).
- 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.
- Ketorolac tromethamine, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of 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 (GI) Effects, Risk of GI Ulceration, Bleeding, and Perforation**).

- Ketorolac tromethamine, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
- 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.
- 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**).
- In late pregnancy, as with other NSAIDs, ketorolac tromethamine should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

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

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.

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 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 dosed intravenously or intramuscularly was given with two doses of 5,000 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 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 higher than the users of either drug alone.

Aspirin

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

Diuretics

Clinical studies, as well as 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 **probenecid** resulted in decreased clearance and volume of distribution 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 attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

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

ACE Inhibitors/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 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/intramuscular and **nondepolarizing muscle relaxants** that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Selective Serotonin Reuptake Inhibitors (SSRIs)

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

Carcinogenesis, Mutagenesis, 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 recommended 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 tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1,590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

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

Pregnancy

Teratogenic Effects

Pregnancy Category C

Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine tablets at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1 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.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. Oral doses of ketorolac tromethamine tablets at 1.5 mg/kg (0.14 times the human AUC), administered after gestation day 17, caused dystocia and higher pup mortality in rats.

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

Labor and Delivery

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

Nursing Mothers

Limited data from one published study that included 10 breastfeeding women 2 to 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 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 to 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 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 (GI) Effects – Risk of GI 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 Fresenius 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 GI ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure (see **Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION**). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

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

Gastrointestinal (GI) experiences including:			
abdominal pain	constipation/diarrhea	dyspepsia	
flatulence	GI fullness	GI ulcers (gastric/duodenal)	
gross bleeding/perforation	heartburn	nausea*	
stomatitis	vomiting		
Other experiences:			
abnormal renal function	anemia	dizziness	
drowsiness	edema	elevated liver enzymes	
headaches*	hypertension	increased bleeding time	
injection site pain	pruritus	purpura	
rashes	tinnitus	sweating	

*Incidence greater than 10%

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

Body as a Whole: fever, infections, sepsis

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

Dermatologic: alopecia, photosensitivity, urticaria
Gastrointestinal: anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, renal bleeding
Hemic and Lymphatic: ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia

Metabolic and Nutritional: weight change

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

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

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

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

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

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

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

Hemic and Lymphatic: agranulocytosis, aplastic anemia, hemolytic anemia, lymphadenopathy, pancytopenia, postoperative wound hemorrhage (rarely requiring blood transfusion – see **Boxed WARNING, WARNINGS, and PRECAUTIONS**)
Metabolic and Nutritional: hyperglycemia, hyperkalemia, hyponatremia
Nervous System: aseptic meningitis, convulsions, coma, psychosis

Respiratory: bronchospasm, respiratory depression, pneumonia

Special Senses: conjunctivitis

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

Postmarketing Surveillance Study

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

Table 3: Incidence of Clinically Serious GI Bleeding as Related to Age, Total Daily Dose, and History of GI Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine Injection				
A. Adult Patients without History of PUB				
Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%
B. Adult Patients with History of PUB				
Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25%

OVERDOSAGE:

Symptoms and Signs

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

Treatment

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

Single overdoses of ketorolac tromethamine have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers, and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing.

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 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 or 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.

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 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 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.
- 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.

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 ≥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