

Ketorolac Tromethamine Injection, USP
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 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 intestine, 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. These risks may occur early in treatment and may increase with duration of use (see **WARNINGS** and **PRECAUTIONS**).

Ketorolac tromethamine 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 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 countermeasures 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 **DOSEAGE AND ADMINISTRATION**) and for patients with moderately elevated serum creatinine (see **WARNINGS**). Doses of ketorolac tromethamine injection are not to exceed 10 mg total dose per day in these patients.

DOSEAGE AND ADMINISTRATION

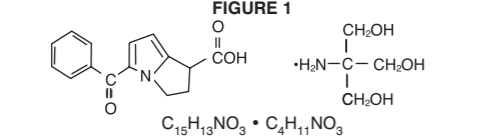
Ketorolac Tromethamine Tablets

Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine injection, and the combined duration of use of ketorolac tromethamine injection and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.

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

DESCRIPTION

Ketorolac Tromethamine Injection, USP is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (+)-5-benzoyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]1*H*-carboxylic acid, 2-(4-propylamino-2-hydroxyethyl)-1,3-propanediol (1:1), and the structural formula is presented in Figure 1.



Ketorolac tromethamine is a racemic mixture of [-]-S- and [+]-R-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.40.

Ketorolac Tromethamine Injection, USP is available for intravenous (IV) or intramuscular (IM) administration as: 15 mg in 1 mL (1.5%) and 30 mg in 1 mL (3%) in sterile solution; 60 mg in 2 mL (3%) of ketorolac tromethamine in sterile solution is available for intramuscular administration only. The solutions contain 0.1% citric acid, 10% (w/v) alcohol, USP; and 6.66 mg, 4.36 mg, and 8.70 mg, respectively, of sodium chloride in sterile water. The pH range is 6.9 to 7.9 and is adjusted with sodium hydroxide and/or hydrochloric acid. The sterile solutions are clear and slightly yellow in color.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

completely understood but may be related to prostaglandin synthase inhibition. The biological activity of ketorolac tromethamine is associated with the S-form.

Ketorolac tromethamine possesses no sedative or anxiolytic properties.

The peak analgesic effect of ketorolac tromethamine occurs within 2 to 3 hours and is not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route is in the duration of analgesia.

Pharmacokinetics

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

Comparison of 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.

Pharmacokinetic Parameters (units)	Oral ¹		Intramuscular* ²		Intravenous Bolus ³	
	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 _{avg} ⁴ (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 _d ⁵ (L/kg)	~0.175±0.039				0.210±0.044	

% 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

[†] 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_{max} and T_{max} data

¹ Time-to-peak plasma concentration

² Peak plasma concentration

³ Trough plasma concentration

⁴ Average plasma concentration

⁵ Volume of distribution

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 intramuscular 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 as much as in the feces, as unchanged drug. 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 renal volume of distribution. 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 4 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.

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 Table 2: The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of Ketorolac Tromethamine (Intramuscular¹ and Ora²) 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				
Intramuscular (n = 54)				
mean age = 32, range = 18-60	0.023	0.025	5.3	5.3
Oral (n = 77)	(0.010-0.046)	(0.013-0.050)	(3.5-9.2)	(2.4-9)
mean age = 32, range = 20-60				
Healthy Elderly Subjects				
Intramuscular (n = 13), Oral (n = 12)	0.019	0.024	7	6.1
mean age = 72, range = 65-78	(0.013-0.034)	(0.018-0.034)	(4.7-8.6)	(4.3-7.6)
Patients with Hepatic Dysfunction				
Intramuscular and Oral (n = 7)	0.029	0.033	5.4	4.5
mean age = 51, range = 43-64	(0.013-0.066)	(0.019-0.051)	(2.2-6.9)	(1.6-7.6)
Patients with Renal Impairment				
Intramuscular (n = 25), Oral (n = 9)				
serum creatinine = 1.5-5.0 mg/dL, mean age (Intramuscular) = 54, range = 35-71				
mean age (Oral) = 57, range = 39-70	0.015	0.016	10.3	10.8
	(0.005-0.043)	(0.007-0.052)	(5.9-19.2)	(3.4-18.9)
Renal Dialysis Patients				
Intramuscular and Oral (n = 9)	0.016	0.016	13.6	–
mean age = 40, range = 27-63	(0.003-0.036)	–	(8.0-39.1)	–

¹ Estimated from 30 mg single intramuscular doses of ketorolac tromethamine

² Estimated from 10 mg single oral doses of ketorolac tromethamine

³ Liters/hour/kilogram

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

CLINICAL STUDIES

The concomitant use of ketorolac tromethamine and pentoxifyline is contraindicated.

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

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.

The most serious risks associated with ketorolac tromethamine are:

• **Gastrointestinal Effects – Risk of Ulceration, Bleeding and Perforation:** Ketorolac tromethamine is contraindicated in patients with a history of ulceration, bleeding, or perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy.

The incidence and severity of gastrointestinal complications increases with increasing dose 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 recent use of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse reaction is suspected. This should include discontinuation of ketorolac tromethamine until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn’s disease) as their condition may be exacerbated.

Hemorrhage

Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently, therefore, physicians who administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and therapy that affects hemostasis, including prophylactic low-dose heparin (2500-5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with increased risk of bleeding. Use data from such studies are available, physicians should carefully weigh the benefits against the risks, and use such concomitant therapy in these patients only extremely cautiously. Patients receiving therapy that affects hemostasis should be monitored closely.

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the peri-operative use of intravenous or intramuscular dosing of ketorolac tromethamine. Therefore, peri-operative use is contraindicated.

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of ketorolac tromethamine should be avoided and postoperative use may be undertaken with caution when hemostasis is critical (see **CONTRAINDICATIONS**).

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the 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 **DOSEAGE AND ADMINISTRATION**) and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, interstitial nephritis and nephrotic syndrome.

Impaired Renal Function

Ketorolac tromethamine is contraindicated in patients with serum creatinine concentrations indicating advanced renal impairment (see **CONTRAINDICATIONS**). Ketorolac tromethamine should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Because patients with underlying renal insufficiency are at increased risk of developing acute renal decompensation or failure, the risks and benefits should be assessed prior to giving ketamine to these patients.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ketorolac tromethamine.

Ketorolac tromethamine should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who also experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS – Pre-existing Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

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 frequently reported as soon as 48 hours after the initiation of treatment. 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

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 result 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

Aspirin is a nonsteroidal anti-inflammatory drug 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 or intramuscular or intravenous dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients. Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Advise patients to be alert for the symptoms of cardiovascular 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**).

3. **Serious Skin Reactions, including DRESS**
Advise patients to stop taking ketorolac tromethamine immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible (see **WARNINGS**).

4. Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur (see **WARNINGS**).

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). 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**).

7. **Fetal Toxicity**
Inform pregnant women to avoid use of ketorolac tromethamine and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with ketorolac tromethamine is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours (see **WARNINGS, Fetal Toxicity, PRECAUTIONS: Pregnancy**).

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

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, 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 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 1590 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

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

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

Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and, in some cases, neonatal renal impairment.

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, 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 birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

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

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

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

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with the cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the 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 ketorolac tromethamine should be considered.

Nursing Mothers

Limited data from one published study that included 10 breast-feeding women 2-6 days postpartum showed low levels of ketorolac in breast milk and were undetectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 mg of ketorolac tromethamine, the maximum milk 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 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**), they are also more sensitive to the dose-related adverse effects of NSAIDs (see **WARNINGS – Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**), extreme caution and reduced dosages (see **DOSAGE AND ADMINISTRATION**) and careful clinical monitoring must be used when treating the elderly with ketorolac tromethamine.

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact 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	
<i>Other experiences:</i>		
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, post operative wound hemorrhage (rarely requiring blood transfusion — see **Boxed WARNING, WARNINGS, and PRECAUTIONS**)

Metabolic and Nutritional: hyperglycemia, hyperkalemia, hyponatremia

Nervous System: aseptic meningitis, convulsions, coma, psychosis

Respiratory: bronchospasm, respiratory depression, pneumonia

Special Senses: conjunctivitis

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

Postmarketing Surveillance Study
A large postmarketing observational, nonrandomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (GI) bleeding was dose-dependent (see Tables 3A and 3B).

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 G.I. 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%	25.0%

OVERDOSAGE

Symptoms and Signs

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

Treatment

Patients should be managed by symptomatic and supportive care following a NSAIDs overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 g to 100 g in adults, 1 g/kg to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing.

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 treat with 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 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 intravenously or intramuscularly. 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, do not increase the dose or the frequency of ketorolac tromethamine. Consideration should be given to supplementing these regimens with low doses of opioids “prn” unless otherwise contraindicated.

Pharmaceutical Information for Ketorolac Tromethamine Injection

Ketorolac tromethamine injection should not be mixed in a small volume (e.g., in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution. **NOTE:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Ketorolac Tromethamine Injection, USP is supplied as follows:

FOR INTRAMUSCULAR OR INTRAVENOUS USE.

Product Code	Unit of Sale	Strength	Each
160101	NDC 63323-161-01 Unit of 25	15 mg per mL	NDC 63323-161-00 1 mL fill in a 2 mL single dose vial
RF160201	NDC 63323-162-51 Unit of 25	30 mg per mL	NDC 63323-162-11 1 mL fill in a 2 mL single dose vial This product contains an RFID.
160201	NDC 633		