KETOROCAINE L KIT- ketorolac tromethamine, lidocaine hydrochloride, povidine iodine
Asclemed USA, Inc.

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Ketorolac

Tromethamine

Injection, USP
FOR IV/IM USE (15 mg and 30 mg)
FOR IM USE ONLY (60 mg)
Rx only
WARNING

Ketorolac trometamine, 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 trometamine is indicated only as continuation treatment following IV or IM dosing of ketorolac trometamine, if necessary. The total combined duration of use of oral ketorolac trometamine and ketorolac trometamine injection should not exceed 5 days.

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

GASTROINTESTINAL RISK
- Ketorolac trometamine 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 trometamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

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

RENAL RISK
- Ketorolac trometamine 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 trometamine 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 trometamine 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 trometamine injection (see CONTRAINDICATIONS and WARNINGS). Ketorolac trometamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac trometamine or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

INTRATHECAL OR EPIDURAL ADMINISTRATION
- Ketorolac trometamine is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol content.

RISK DURING LABOR AND DELIVERY
- The use of ketorolac trometamine 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 structural formula is presented in Figure 1.

![Figure 1: Structural formula of ketorolac tromethamine](image)

C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3

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 IM administration only. The solutions contain 10% (w/v) alcohol, USP, and 6.68 mg, 4.35 mg, and 8.70 mg, respectively, of sodium chloride in sterile water. The pH range is 6.9 to 7.9 and is adjusted with sodium hydroxide and/or hydrochloric acid. The sterile solutions are clear and slightly yellow in color.
**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models. The mechanism of action of ketorolac, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. The biological activity of ketorolac tromethamine is associated with the S-form.

Ketorolac tromethamine possesses no sedative or anxiolytic properties.

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

**Pharmacokinetics**

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

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

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

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

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (units)</th>
<th>Oral†</th>
<th>Intramuscular*</th>
<th>Intravenous Bolus ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability (extent)</strong></td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T</strong>&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;1&lt;/sup&gt; (min)</td>
<td>44±34</td>
<td>33±21**</td>
<td>44±29</td>
</tr>
<tr>
<td><strong>C</strong>&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;2&lt;/sup&gt; (mcg/mL) [Single-dose]</td>
<td>0.87±0.22</td>
<td>1.14±0.32**</td>
<td>2.42±0.68</td>
</tr>
<tr>
<td><strong>C</strong>&lt;sub&gt;max&lt;/sub&gt; (mcg/mL) [steady state qid]</td>
<td>1.05±0.26**</td>
<td>1.56±0.44**</td>
<td>3.11±0.87**</td>
</tr>
<tr>
<td><strong>C</strong>&lt;sub&gt;min&lt;/sub&gt;&lt;sup&gt;3&lt;/sup&gt; (mcg/mL) [steady state qid]</td>
<td>0.29±0.07**</td>
<td>0.47±0.13**</td>
<td>0.93±0.26**</td>
</tr>
<tr>
<td><strong>C</strong>&lt;sub&gt;avg&lt;/sub&gt;&lt;sup&gt;4&lt;/sup&gt; (mcg/mL) [steady state qid]</td>
<td>0.59±0.2**</td>
<td>0.94±0.29**</td>
<td>1.88±0.59**</td>
</tr>
<tr>
<td><strong>V</strong>&lt;sub&gt;B&lt;/sub&gt;&lt;sup&gt;5&lt;/sup&gt; (L/kg)</td>
<td>————</td>
<td>0.175±0.039</td>
<td>————</td>
</tr>
<tr>
<td>% Dose metabolized = &lt;50%</td>
<td>% Dose excreted in feces = 6%</td>
<td>% Dose excreted in urine = 91%</td>
<td></td>
</tr>
<tr>
<td>% Plasma protein binding = 99%</td>
<td><strong>1</strong>Time-to-peak plasma concentration</td>
<td><strong>2</strong>Peak plasma concentration</td>
<td></td>
</tr>
<tr>
<td><strong>3</strong>Trough plasma concentration</td>
<td><strong>4</strong>Average plasma concentration</td>
<td><strong>5</strong>Volume of distribution</td>
<td></td>
</tr>
</tbody>
</table>

† Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
* Derived from IM pharmacokinetic studies in 54 normal volunteers
‡ Derived from IV 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**<sub>max</sub> and **T**<sub>max</sub> data

**Linear Kinetics**
In adults, following administration of single ORAL, IM or IV doses of ketorolac tromethamine in the
recommended dosage ranges, the clearance of the racemate does not change. This implies that the
pharmacokinetics of ketorolac tromethamine in adults, following single or multiple IM, IV or
recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses,
there is a proportional increase in the concentrations of free and bound racemate.

Distribution

The mean apparent volume (V_\text{app}) 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 IV bolus, every 6 hours, for 5 days, to healthy subjects
(n = 13), showed no significant difference in C_{\text{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).

Kinetics in Special Populations

Geriatric Patients

Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5
to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years) (see
Table 2). There was little difference in the C_{\text{max}} for the two groups (elderly, 2.52 mcg/mL ± 0.77;
young, 2.99 mcg/mL ± 1.03) (see PRECAUTIONS – Geriatric Use).

Pediatric Patients

Limited information is available regarding the pharmacokinetics of dosing of ketorolac tromethamine in
the pediatric population. Following a single intravenous bolus dose of 0.5 mg/kg in 10 children 4 to 8
years old, the half-life was 5.8 ± 1.6 hours, the average clearance was 0.042 ± 0.01 L/hr/kg, the volume of distribution during the terminal phase (V₁) was 0.34 ± 0.12 L/kg and the volume of distribution at steady state (Vss) was 0.26 ± 0.08 L/kg. The volume of distribution and clearance of ketorolac in pediatric patients was higher than those observed in adult subjects (see Table 1). There are no pharmacokinetic data available for administration of ketorolac tromethamine by the IM route in pediatric patients.

**Renal Insufficiency**

Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r = 0.5).

In patients with renal disease, the AUC∞ 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∞-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∞ and Cmax, in 7 patients with liver disease compared to healthy volunteers (see PRECAUTIONS – Hepatic Effects and Table 2).

**Race**

Pharmacokinetic differences due to race have not been identified.

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

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

¹ IM = Intramuscular
² ORAL = Oral
³ Clearance [in L/hr/kg]
CLINICAL STUDIES

Adult Patients

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

INDICATIONS AND USAGE

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

Acute Pain in Adult Patients

Ketorolac tromethamine is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with IV or IM dosing of ketorolac tromethamine, and oral ketorolac tromethamine is to be used only as continuation treatment, if necessary.

The total combined duration of use of ketorolac tromethamine injection and oral ketorolac tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS). Patients should be switched to alternative analgesics as soon as possible, but 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 administered in the same syringe (see DOSAGE AND ADMINISTRATION – Pharmaceutical Information for Ketorolac Tromethamine Injection).

CONTRAINDICATIONS

(see also Boxed WARNING)

Ketorolac Tromethamine is contraindicated in patients with previously demonstrated hypersensitivity to ketorolac tromethamine.

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

Ketorolac tromethamine should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like
reactions to NSAIDs have been reported in such patients (see WARNINGS – Anaphylactoid Reactions, and PRECAUTIONS – Pre-existing Asthma).

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

Ketorolac tromethamine is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

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

Ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.

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

Ketorolac tromethamine is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events.

The concomitant use of ketorolac tromethamine and probenecid is contraindicated.

The concomitant use of ketorolac tromethamine and pentoxifylline is contraindicated.

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

**WARNINGS**

(See also Boxed WARNING.)

The total combined duration of use of oral ketorolac tromethamine and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients.

The most serious risks associated with ketorolac tromethamine are:

- **Gastrointestinal Effects – Risk of Ulceration, Bleeding and Perforation:** Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or gastrointestinal (GI) bleeding. Ketorolac tromethamine can cause serious GI adverse events including bleeding, ulceration and perforation, of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine.

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

The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with ketorolac tromethamine. Do not use ketorolac tromethamine for more than five days.

However, even short-term therapy is not without risk. In addition to past history of ulcer disease, other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids, or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

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

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

**Hemorrhage**

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

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

**Renal Effects**

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

**Anaphylactoid Reactions**

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

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation). Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

Hypertension

NSAIDs, including ketorolac tromethamine, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ketorolac tromethamine, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension or similar conditions.

Skin Reactions

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

Pregnancy

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

PRECAUTIONS

General

Ketorolac tromethamine cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
The pharmacological activity of ketorolac tromethamine in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

**Hepatic Effects**

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

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

**Hematologic Effects**

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

**Pre-existing Asthma**

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

**Information for Patients**

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

Physicians, when prescribing ketorolac tromethamine, should inform their patients or their guardians of the potential risks of ketorolac tromethamine treatment (see Boxed WARNING, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections), instruct patients to seek medical advice if they develop treatment-related adverse events, and advise patients not to give oral ketorolac tromethamine to other family members and to discard any unused drug. Remember that the total combined duration of use of oral ketorolac tromethamine and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients. 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. Ketorolac tromethamine, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur
without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Cardiovascular Effects).

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 signs 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. 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 skin rash and blisters, fever, or other signs of hypersensitivity such as itching, 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.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

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. 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 IV or IM 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.

**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 IV/IM 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 IM or IV 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

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 (1.0 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.

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 2-6 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) who are also more sensitive to the dose-related adverse effects of NSAIDs (see WARNINGS – Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation), extreme caution and reduced dosages (see DOSAGE AND ADMINISTRATION) and careful clinical monitoring must be used when treating the elderly with ketorolac tromethamine.

ADVERSE REACTIONS

Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure (see Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

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

<table>
<thead>
<tr>
<th>Gastrointestinal (GI) experiences including:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>abdominal pain</td>
<td>constipation/diarrhea</td>
<td>dyspepsia</td>
</tr>
<tr>
<td>flatulence</td>
<td>GI fullness</td>
<td>GI ulcers (gastric/duodenal)</td>
</tr>
<tr>
<td>gross bleeding/perforation</td>
<td>heartburn</td>
<td>nausea*</td>
</tr>
<tr>
<td>stomatitis</td>
<td>vomiting</td>
<td></td>
</tr>
<tr>
<td>Other experiences:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal renal function</td>
<td>anemia</td>
<td>dizziness</td>
</tr>
<tr>
<td>drowsiness</td>
<td>edema</td>
<td>elevated liver enzymes</td>
</tr>
<tr>
<td>headaches*</td>
<td>hypertension</td>
<td>increased bleeding time</td>
</tr>
</tbody>
</table>
Additional adverse experiences reported occasionally (<1% in patients taking ketorolac tromethamine or other NSAIDs in clinical trials) include:

**Body as a Whole:** fever, infections, sepsis

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

**Dermatologic:** alopecia, photosensitivity, urticaria

**Gastrointestinal:** anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, rectal bleeding

**Hemic and Lymphatic:** ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia

**Metabolic and Nutritional:** weight change

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

**Reproductive, female:** infertility

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

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

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

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

**Body as a Whole:** angioedema, death, hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see **WARNINGS**), myalgia

**Cardiovascular:** arrhythmia, bradycardia, chest pain, flushing, hypotension, myocardial infarction, vasculitis

**Dermatologic:** exfoliative dermatitis, erythema multiforme, Lyell’s syndrome, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

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

**Hemic and Lymphatic:** agranulocytosis, aplastic anemia, hemolytic anemia, lymphadenopathy, pancytopenia, post operative wound hemorrhage (rarely requiring blood transfusion — see **Boxed WARNING, WARNINGS, and PRECAUTIONS**)

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

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

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

**Special Senses:** conjunctivitis

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

**Postmarketing Surveillance Study**

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

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

<table>
<thead>
<tr>
<th>A. Adult Patients without History of PUB</th>
<th>Total Daily Dose of Ketorolac Tromethamine Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Patients</td>
<td>≤60 mg</td>
</tr>
<tr>
<td>&lt;65 years of age</td>
<td>0.4%</td>
</tr>
<tr>
<td>≥65 years of age</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Adult Patients with History of PUB</th>
<th>Total Daily Dose of Ketorolac Tromethamine Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Patients</td>
<td>≤60 mg</td>
</tr>
<tr>
<td>&lt;65 years of age</td>
<td>2.1%</td>
</tr>
<tr>
<td>≥65 years of age</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

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

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

Use minimum effective dose for the individual patient.
**Total duration of treatment in adult patients:** the combined duration of use of IV or IM dosing of ketorolac tromethamine and oral ketorolac tromethamine is not to exceed 5 days.

**KETOROLAC TROMETHAMINE INJECTION**

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

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

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

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

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

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

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

**Pharmaceutical Information for Ketorolac Tromethamine Injection**

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

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

**HOW SUPPLIED**

Ketorolac Tromethamine Injection, USP is supplied as follows:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Container Description</th>
<th>Concentration (mg/mL)</th>
<th>Fill Volume/Container Size</th>
<th>Total Ketorolac Tromethamine (Per Container)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0409-3793-01</td>
<td>Single-Dose Glass</td>
<td>15 mg/mL</td>
<td>1 mL/2 mL</td>
<td>15 mg</td>
</tr>
</tbody>
</table>
Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

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

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:
- with longer use of NSAID medicines
- in people who have heart disease

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

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:
- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

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

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:
- different types of arthritis
- menstrual cramps and other types of short-term pain

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

**Do not take an NSAID medicine:**
- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

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

**Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant.

**NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

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

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

**Other side effects include:**
- heart attack
- stomach pain
- constipation
- diarrhea
- gas
- heartburn
- nausea
- vomiting
- dizziness

**Get emergency help right away if you have any of the following symptoms:**
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat
Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

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

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

### NSAID medicines that need a prescription

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to www.hospira.com or call 1-800-615-0187.

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

Revised: 12/2011

EN-3485

Hospira, Inc., Lake Forest, IL 60045 USA

AQUEOUS SOLUTIONS FOR INFILTRATION
AND NERVE BLOCK

Ampul

Plastic Multiple-dose Flipped Vial

Glass Teartop Vial

Rx only

DESCRIPTION

Lidocaine Hydrochloride Injection, USP is a sterile, nonpyrogenic solution of lidocaine hydrochloride in water for injection for parenteral administration in various concentrations with characteristics as follows:

<table>
<thead>
<tr>
<th>Concentration</th>
<th>0.5%</th>
<th>1%</th>
<th>1.5%</th>
<th>2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/mL lidocaine HCl (anhyd.)</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>mg/mL sodium chloride</td>
<td>8</td>
<td>7</td>
<td>6.5</td>
<td>6</td>
</tr>
</tbody>
</table>

Multiple-dose vials contain 0.1% of methylparaben added as preservative. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. The pH is 6.5 (5.0 to 7.0). See HOW SUPPLIED section for various sizes and strengths.

Lidocaine is a local anesthetic of the amide type.

Lidocaine Hydrochloride, USP is chemically designated 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide monohydrochloride monohydrate, a white powder freely soluble in water. The molecular weight is 288.82. It has the following structural formula:

![Structural formula of Lidocaine Hydrochloride](image)

The semi-rigid vial used for the plastic vials is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper drug concentration.
CLINICAL PHARMACOLOGY

Mechanism of action: Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

Hemodynamics: Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

Pharmacokinetics and metabolism: Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey arterial blood levels of 18-21 mcg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE

Lidocaine Hydrochloride Injection, USP is indicated for production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks, when the accepted procedures for these techniques as described in standard textbooks are observed.

CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of
the amide type.

WARNINGS

LIDOCAINE HYDROCHLORIDE INJECTION, FOR INFILTRATION AND NERVE BLOCK, SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Local anesthetic solutions containing antimicrobial preservatives (e.g., methylparaben) should not be used for epidural or spinal anesthesia because the safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental.

Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs and symptoms of methemoglobinemia may occur immediately or may be delayed some hours after exposure and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine and any other oxidizing agents. Depending on the severity of the symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

PRECAUTIONS

General:
The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various regional anesthetic procedures.

Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Syringe aspirations should also be performed before and during each supplemental injection when using indwelling catheter techniques. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and that the patient be monitored for central nervous system toxicity and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions that contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Lidocaine should also be used with caution in patients with severe shock or heart block. Lumbar and caudal epidural anesthesia should be used with extreme caution in persons with the following conditions: existing neurological disease, spinal deformities, septicemia and severe hypertension.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient’s state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for the management of malignant hyperthermia should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Proper tourniquet technique, as described in publications and standard textbooks, is essential in the performance of intravenous regional anesthesia. Solutions containing epinephrine or other vasoconstrictors should not be used for this technique.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to
para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

**Use in the Head and Neck Area:** Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injections of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded. (See **DOSAGE AND ADMINISTRATION**).

**Information for Patients:**

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body following proper administration of epidural anesthesia.

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

**Clinically Significant Drug Interactions:**

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (for the treatment of hypotension related to obstetric blocks) and ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Patients that are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following oxidizing agents:

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates/Nitrites</td>
<td>nitroglycerin, nitroprusside, nitric oxide, nitrous oxide</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine, ropivacaine</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>cyclophosphamide, flutamide, rasburicase, ifosfamide, hydroxyurea</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>chloroquine, primaquine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>phenytoin, sodium valproate, phenobarbital</td>
</tr>
<tr>
<td>Other drugs</td>
<td>acetaminophen, metoclopramide, sulfa drugs (i.e., sulfasalazine), quinine</td>
</tr>
</tbody>
</table>
Drug Laboratory Test Interactions:
The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination without isoenzyme separation as a diagnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy:
Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Labor and Delivery:
Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (See CLINICAL PHARMACOLOGY—Pharmacokinetics). The potential for toxicity depends upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient’s legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study, paracervical block anesthesia was associated with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. However, spinal and epidural anesthesia have also been reported to prolong the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long-term significance of these observations is unknown. Fetal bradycardia may occur in 20 to 30 percent of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering paracervical block in prematurity, toxemia of pregnancy and fetal distress. Careful adherence to recommended dosage is of the utmost importance in obstetrical paracervical block. Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Case reports of maternal convulsions and cardiovascular collapse following use of some local
anesthetics for paracervical block in early pregnancy (as anesthesia for elective abortion) suggest that systemic absorption under these circumstances may be rapid. The recommended maximum dose of each drug should not be exceeded. Injection should be made slowly and with frequent aspiration. Allow a 5-minute interval between sides.

**Nursing Mothers:**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

**Pediatric Use:**

Dosages in pediatric patients should be reduced, commensurate with age, body weight and physical condition. See **DOSAGE AND ADMINISTRATION**.

**ADVERSE REACTIONS**

**Systemic:** Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

**Central Nervous System:** CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

**Cardiovascular System:** Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

**Allergic:** Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

**Neurologic:** The incidences of adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. In a prospective review of 10,440 patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were reported to be about 3 percent each for positional headaches, hypotension and backache; 2 percent for shivering; and less than 1 percent each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the local anesthetic.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally.

These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control, and loss of perineal sensation and sexual
function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anesthetic procedures.

There have been reported cases of permanent injury to extraocular muscles requiring surgical repair following retrobulbar administration.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see ADVERSE REACTIONS, WARNINGS and PRECAUTIONS).

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful monitoring of cardiovascular and respiratory vital signs and the patient’s state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea due to unintended subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The oral LD₅₀ of lidocaine HCl in non-fasted female rats is 459 (346–773) mg/kg (as the salt) and 214 (159–324) mg/kg (as the salt) in fasted female rats.

DOSAGE AND ADMINISTRATION

Table 1 (Recommended Dosages) summarizes the recommended volumes and concentrations of Lidocaine Hydrochloride Injection, USP for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults and refer to the use of epinephrine-free solutions. When larger volumes are required only solutions containing epinephrine should be used, except in those cases where vasopressor drugs may be contraindicated.

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. Lidocaine is not approved for
these recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of anesthesia required, and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for children and for elderly and debilitated patients and patients with cardiac and/or liver disease.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration (i.e., total dose) of local anesthetic used. Thus, an increase in volume and concentration of Lidocaine Hydrochloride Injection will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. However, increasing the volume and concentration of Lidocaine Hydrochloride Injection may result in a more profound fall in blood pressure when used in epidural anesthesia. Although the incidence of side effects with lidocaine is quite low, caution should be exercised when employing large volumes and concentrations, since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

For intravenous regional anesthesia, only the 50 mL single-dose vial containing 0.5% Lidocaine Hydrochloride Injection, USP should be used.

**Epidural Anesthesia**

For epidural anesthesia, only the following available specific products of Lidocaine Hydrochloride Injection by Hospira are recommended:

1% . . . . . . . . . . . . . . . . . . . . . . . . . 30 mL single-dose teartop vials

1.5%. . . . . . . . . . . . . . . . . . . . . . . . . 20 mL single-dose ampuls

2% . . . . . . . . . . . . . . . . . . . . . . . . . 10 mL single-dose ampuls

Although these solutions are intended specifically for epidural anesthesia, they may also be used for infiltration and peripheral nerve block provided they are employed as single dose units. These solutions contain no bacteriostatic agent. In epidural anesthesia, the dosage varies with the number of dermatomes to be anesthetized (generally 2–3 mL of the indicated concentration per dermatome).

**Caudal and Lumbar Epidural Block:** As a precaution against the adverse experiences sometimes observed following unintentional penetration of the subarachnoid space, a test dose such as 2–3 mL of 1.5% lidocaine hydrochloride should be administered at least 5 minutes prior to injecting the total volume required for a lumbar or caudal epidural block. The test dose should be repeated if the patient is moved in a manner that may have displaced the catheter. Epinephrine, if contained in the test dose (10–15 mcg have been suggested), may serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect an evanescent rise in systolic blood pressure. Adequate time should be allowed for onset of anesthesia after administration of each test dose. The rapid injection of a large volume of Lidocaine Hydrochloride Injection through the catheter should be avoided, and, when feasible, fractional doses should be administered.

In the event of the known injection of a large volume of local anesthetic solutions into the subarachnoid space, after suitable resuscitation and if the catheter is in place, consider attempting the recovery of drug by draining a moderate amount of cerebrospinal fluid (such as 10 mL) through the epidural catheter.
Maximum Recommended Dosages

NOTE: The products accompanying this insert do not contain epinephrine.

**Adults:** For normal healthy adults, the individual maximum recommended dose of lidocaine HCl with epinephrine should not exceed 7 mg/kg (3.5 mg/lb) of body weight and in general it is recommended that the maximum total dose not exceed 500 mg. When used without epinephrine, the maximum individual dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight and in general it is recommended that the maximum total dose does not exceed 300 mg. For continuous epidural or caudal anesthesia, the maximum recommended dosage should not be administered at intervals of less than 90 minutes. When continuous lumbar or caudal epidural anesthesia is used for non-obstetrical procedures, more drug may be administered if required to produce adequate anesthesia.

The maximum recommended dose per 90 minute period of lidocaine hydrochloride for paracervical block in obstetrical patients and non-obstetrical patients is 200 mg total. One-half of the total dose is usually administered to each side. Inject slowly five minutes between sides. (See also discussion of paracervical block in **PRECAUTIONS**).

For intravenous regional anesthesia, the dose administered should not exceed 4 mg/kg in adults.

**Children:** It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child’s age and weight. For example, in a child of 5 years weighing 50 lbs., the dose of lidocaine HCl should not exceed 75 — 100 mg (1.5 — 2 mg/lb). The use of even more dilute solutions (i.e., 0.25 — 0.5%) and total dosages not to exceed 3 mg/kg (1.4 mg/lb) are recommended for induction of intravenous regional anesthesia in children.

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conc. (%)</th>
<th>Vol. (mL)</th>
<th>Total Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infiltration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>0.5 or 1.0</td>
<td>1–60</td>
<td>5–300</td>
</tr>
<tr>
<td>Intravenous Regional</td>
<td>0.5</td>
<td>10–60</td>
<td>50–300</td>
</tr>
<tr>
<td><strong>Peripheral Nerve Blocks, e.g.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial</td>
<td>1.5</td>
<td>15–20</td>
<td>225–300</td>
</tr>
<tr>
<td>Dental</td>
<td>2.0</td>
<td>1–5</td>
<td>20–100</td>
</tr>
<tr>
<td>Intercostal</td>
<td>1.0</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>1.0</td>
<td>3–5</td>
<td>30–50</td>
</tr>
<tr>
<td>Pudendal (each side)</td>
<td>1.0</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Paracervical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrical Analgesia (each side)</td>
<td>1.0</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td><strong>Sympathetic Nerve Blocks, e.g.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical (stellate ganglion)</td>
<td>1.0</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Central Neural Blocks</td>
<td></td>
<td>5–10</td>
<td>50–100</td>
</tr>
<tr>
<td>----------------------</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Epidural*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>1.0</td>
<td>20–30</td>
<td>200–300</td>
</tr>
<tr>
<td>Lumbar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesia</td>
<td>1.0</td>
<td>25–30</td>
<td>250–300</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>1.5</td>
<td>15–20</td>
<td>225–300</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>10–15</td>
<td>200–300</td>
</tr>
<tr>
<td>Caudal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrical Analgesia</td>
<td>1.0</td>
<td>20–30</td>
<td>200–300</td>
</tr>
<tr>
<td>Surgical Anesthesia</td>
<td>1.5</td>
<td>15–20</td>
<td>225–300</td>
</tr>
</tbody>
</table>

*Dose determined by number of dermatomes to be anesthetized (2 to 3 mL/dermatome).

THE ABOVE SUGGESTED CONCENTRATIONS AND VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES AND CONCENTRATIONS MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.

Sterilization, Storage and Technical Procedures: Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection as they have been related to incidence of swelling and edema. When chemical disinfection of multi-dose vials is desired, either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of USP grade, contain denaturants which are injurious to rubber and, therefore, are not to be used. It is recommended that chemical disinfection be accomplished by wiping the vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

HOW SUPPLIED

Lidocaine Hydrochloride Injection, USP is supplied as follows:

<table>
<thead>
<tr>
<th>NDC</th>
<th>Container</th>
<th>Concentration</th>
<th>Size</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-4278-01 Glass Teartop Vial</td>
<td>0.5% (5 mg/mL)</td>
<td>50 mL</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>0409-4713-01 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>2 mL (bulk – 400 units)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>0409-4713-65 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>5 mL</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0409-4713-05 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>5 mL (bulk – 400 units)</td>
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<td></td>
</tr>
<tr>
<td>0409-4713-20 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>20 mL</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>0409-4713-32 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>2 mL</td>
<td>20</td>
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</tr>
<tr>
<td>0409-4713-62 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>2 mL (bulk – 800 units)</td>
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<tr>
<td>0409-4713-65 Glass Ampul</td>
<td>1% (10 mg/mL)</td>
<td>5 mL (bulk – 800 units)</td>
<td>50</td>
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<tr>
<td>0409-4279-02 Glass Teartop Vial</td>
<td>1% (10 mg/mL)</td>
<td>30 mL</td>
<td>300</td>
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<tr>
<td>0409-4270-01 Sterile Glass Teartop Vial</td>
<td>1% (10 mg/mL)</td>
<td>30 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4776-01 Glass Ampul</td>
<td>1.5% (15 mg/mL)</td>
<td>20 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4056-01 Sterile Glass Ampul</td>
<td>1.5% (15 mg/mL)</td>
<td>20 mL</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>0409-4282-01 Glass Ampul</td>
<td>2% (20 mg/mL)</td>
<td>2 mL</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>0409-4282-02 Glass Ampul</td>
<td>2% (20 mg/mL)</td>
<td>10 mL</td>
<td>200</td>
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</tr>
<tr>
<td>Multiple-dose:</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0409-4275-01 Plastic Fliptop Vial</td>
<td>0.5% (5 mg/mL)</td>
<td>50 mL</td>
<td>250</td>
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</tbody>
</table>
### Plastic Fliptop Vial

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Concentration</th>
<th>Volume</th>
<th>Units</th>
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</thead>
<tbody>
<tr>
<td>0409-4276-01</td>
<td>Plastic Fliptop Vial</td>
<td>1% (10 mg/mL)</td>
<td>20 mL</td>
<td>200</td>
</tr>
<tr>
<td>0409-4276-02</td>
<td>Plastic Fliptop Vial</td>
<td>1% (10 mg/mL)</td>
<td>50 mL</td>
<td>500</td>
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<tr>
<td>0409-4277-01</td>
<td>Plastic Fliptop Vial</td>
<td>2% (20 mg/mL)</td>
<td>20 mL</td>
<td>400</td>
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<tr>
<td>0409-4277-02</td>
<td>Plastic Fliptop Vial</td>
<td>2% (20 mg/mL)</td>
<td>50 mL</td>
<td>1000</td>
</tr>
</tbody>
</table>

Single-dose products are preservative-free.

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

Lidocaine Hydrochloride Injection, USP solutions packaged in ampuls and glass teartop vials may be autoclaved one time only. Autoclave at 15 pounds pressure, 121°C (250°F) for 15 minutes. **DO NOT AUTOCLAVE PRODUCT IN PLASTIC VIALS.**

Revised: February, 2010

Printed in USA EN-2421

Hospira, Inc., Lake Forest, IL 60045 USA

### Section Text

**Active Ingredient** | **Purpose**
---|---
Povidone Iodine 10% v/v | Antiseptic

**Purpose:**

- First aid antiseptic to help prevent skin infection in minor cuts, scrapes and burns.
- For preparation of the skin prior to surgery.
- Helps reduce bacteria that can potentially cause skin infections.

**Warnings:**

- **FOR EXTERNAL USE ONLY**

**Do not use:**

- As a first aid antiseptic for more than 1 week.
- In the eyes.
- Over large areas of the body.

**Ask a doctor before use if you have:**

- Deep puncture wounds
- Animal bites
- Serious burns

**Stop Use:**

- If irritation and redness develop
• If condition persists for more than 72 hours, consult a physician.

**Keep Out Of Reach Of Children**

**Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control Center.

**Directions Povidone iodine:**
Tear at notch, remove applicator, use only once.

**As a first aid antiseptic**
• clean affected area
• apply 1 to 3 times daily
• may be covered with a sterile bandage, if bandaged let dry.

**For preoperative patient skin preparation**
• clean area
• apply to operative site prior to surgery using the applicator

**Other information:**
Store at room temperature.
Avoid excessive heat

For use as an
• first aid antiseptic
• pre-operative skin preparation

**Inactive Ingredients**
Inactive ingredients: nonoxynol-9, water

NDC: 76420-771-01 RX Only

**Ketorocaine-L™**

**Kit Contains**
1 Ketorolac Tromethamine Inj., USP 30mg/mL (1mL)
1 Lidocaine HCl Injection, USP 1% Ampule (2mL)
1 Povidone-Iodine Swabsticks (3 Swabs)
2 Isopropyl Alcohol 70% Prep Pads
1 Pair Nitrile Powder Free Sterile Gloves (M)
1 Drape
1 Adhesive Bandage
5 Non Sterile 4x4 Gauze
**Ketorocaine-L**

**Kit Contains**

1. Ketorolac Tromethamine Inj. USP 30mg/mL (1mL)
2. Lidocaine HCl Injection, USP 1% Ampule (2mL)
3. Povidone-Iodine Swabsticks (3 Swabs)
4. Isopropyl Alcohol 70% Prep Pads
5. Pair Nitrile Powder Free Sterile Gloves (M)
6. Drape
7. Adhesive Bandage
8. Non Sterile 4x4 Gauze

**Needles and Syringes Not Included**

1 Dose

Single Use Only

**Distributed by:**

Enovachem™

PHARMACEUTICALS

Torrance, CA 90501

---

**KETOROCAINE L KIT**

ketorolac tromethamine, lidocaine hydrochloride, povidine iodine kit

**Product Information**

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Item Code (Source)</th>
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<tbody>
<tr>
<td>HUMAN PRESCRIPTION DRUG</td>
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**Packaging**

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<th>Package Description</th>
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<th>Marketing End Date</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>1 in 1 CARTON; Type 1: Convenience Kit of Co-Package</td>
<td>08/15/2014</td>
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**Quantity of Parts**

<table>
<thead>
<tr>
<th>Part #</th>
<th>Package Quantity</th>
<th>Total Product Quantity</th>
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</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>1 VIAL, SINGLE-DOSE</td>
<td>1 mL</td>
</tr>
<tr>
<td>Part 2</td>
<td>1 AMPULE</td>
<td>2 mL</td>
</tr>
<tr>
<td>Part 3</td>
<td>1 PACKET</td>
<td>0.9 mL</td>
</tr>
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</table>
Part 1 of 4

KETOROLAC TROMETHAMINE
ketorolac tromethamine injection, solution

Product Information

Route of Administration
INTRAMUSCULAR, INTRAVENOUS

Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>KETOROLAC TROMETHAMINE (UNII: 4EVE5946BQ) (KETOROLAC - UNII:YZI5105V0L)</td>
<td>KETOROLAC TROMETHAMINE</td>
<td>30 mg in 1 mL</td>
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Inactive Ingredients

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>ALCOHOL (UNII: 3K9958V90M)</td>
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</tr>
<tr>
<td>WATER (UNII: 059QF0KO0R)</td>
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</tr>
<tr>
<td>SODIUM CHLORIDE (UNII: 451W47IQ8X)</td>
<td></td>
</tr>
<tr>
<td>SODIUM HYDROXIDE (UNII: 55X04QC32I)</td>
<td></td>
</tr>
<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
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Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
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<th>Marketing End Date</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>1 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product</td>
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Marketing Information

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<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
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<tbody>
<tr>
<td>ANDA</td>
<td>ANDA074802</td>
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Part 2 of 4

LIDOCAINE HYDROCHLORIDE
lidocaine hydrochloride injection, solution

Product Information
### Active Ingredient/Active Moiety

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<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
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<tbody>
<tr>
<td>LIDOCAINE HYDROCHLORIDE (UNII: V13007Z41A)</td>
<td>LIDOCAINE HYDROCHLORIDE ANHYDROUS</td>
<td>10 mg in 1 mL</td>
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### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM CHLORIDE (UNII: 451W47IQ8X)</td>
<td></td>
</tr>
<tr>
<td>WATER (UNII: 059QF0KO0R)</td>
<td></td>
</tr>
<tr>
<td>SODIUM HYDROXIDE (UNII: 55X04QC32I)</td>
<td></td>
</tr>
<tr>
<td>HYDROCHLORIC ACID (UNII: QTT17582CB)</td>
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### Packaging

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<th>Marketing End Date</th>
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<td>2 mL in 1 AMPULE; Type 0: Not a Combination Product</td>
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### Marketing Information

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### Part 3 of 4

**POVIDINE IODINE**

povidine iodine swab

### Product Information

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### Active Ingredient/Active Moiety

<table>
<thead>
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<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Povidone-Iodine (UNII: 85H0HZU99M) (IODINE - UNII:9679TC07X4)</td>
<td>IODINE</td>
<td>10 mg in 1 mL</td>
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### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONOXYNOL-9 (UNII: 48Q180SH9T)</td>
<td></td>
</tr>
</tbody>
</table>
### Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>0.9 mL in 1 PACKET; Type 0: Not a Combination Product</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC monograph final</td>
<td>part333C</td>
<td>05/10/2010</td>
<td></td>
</tr>
</tbody>
</table>

### Part 4 of 4

**ISOPROPYL ALCOHOL**

isopropyl alcohol swab

### Product Information

**Route of Administration**

TOPICAL

### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)</td>
<td>ISOPROPYL ALCOHOL</td>
<td>70 mL in 100 mL</td>
</tr>
</tbody>
</table>

### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATER (UNII: 059QF0KO0 R)</td>
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</tbody>
</table>

### Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
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<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>5 mL in 1 POUCH; Type 0: Not a Combination Product</td>
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### Marketing Information

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>OTC monograph not final</td>
<td>part333A</td>
<td>01/01/2007</td>
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### Marketing Information
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>unapproved drug other</td>
<td></td>
<td>08/15/2014</td>
<td></td>
</tr>
</tbody>
</table>

**Labeler** - Asclemed USA, Inc. (059888437)

Revised: 11/2018

Asclemed USA, Inc.