



TORADOL<sup>®</sup> ORAL

(ketorolac tromethamine tablets)

R<sub>x</sub> only

**WARNING**

TORADOL<sup>ORAL</sup> (ketorolac tromethamine), a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days in adults), management of moderately severe acute pain that requires analgesia at the opioid level and only as continuation treatment following IV or IM dosing of ketorolac tromethamine, if necessary. The total combined duration of use of TORADOL<sup>ORAL</sup> and ketorolac tromethamine should not exceed 5 days.

TORADOL<sup>ORAL</sup> is not indicated for use in pediatric patients and it is NOT indicated for minor or chronic painful conditions. Increasing the dose of TORADOL<sup>ORAL</sup> beyond a daily maximum of 40 mg in adults will not provide better efficacy but will increase the risk of developing serious adverse events.

**GASTROINTESTINAL RISK**

■ Ketorolac tromethamine, including TORADOL 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, TORADOL 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 TRIALS**).

■ TORADOL is CONTRAINDICATED for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

**RENAL RISK**

■ TORADOL 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**

■ TORADOL 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**).

44 **TORADOL is CONTRAINDICATED as prophylactic analgesic before any major**  
45 **surgery.**

46  
47 **RISK DURING LABOR AND DELIVERY**

- 48 ■ The use of TORADOL in labor and delivery is contraindicated because it may  
49 adversely affect fetal circulation and inhibit uterine contractions. The use of  
50 TORADOL is contraindicated in nursing mothers because of the potential adverse  
51 effects of prostaglandin-inhibiting drugs on neonates.

52  
53 **CONCOMITANT USE WITH NSAIDS**

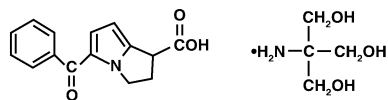
- 54 ■ TORADOL is CONTRAINDICATED in patients currently receiving aspirin or NSAIDs  
55 because of the cumulative risk of inducing serious NSAID-related side effects.

56  
57 **SPECIAL POPULATIONS**

- 58 ■ Dosage should be adjusted for patients 65 years or older, for patients under 50 kg  
59 (110 lbs) of body weight (see **DOSAGE AND ADMINISTRATION**) and for  
60 patients with moderately elevated serum creatinine (see **WARNINGS**).

61  
62 **DESCRIPTION**

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



68 Ketorolac tromethamine is a racemic mixture of [-]S and [+]R ketorolac tromethamine.  
69 Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in  
70 water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition  
71 coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41. Its  
72 molecular formula is C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>.

73 TORADOL<sup>ORAL</sup> is available as round, white, film-coated, red-printed tablets. Each tablet  
74 contains 10 mg ketorolac tromethamine, the active ingredient, with added lactose,  
75 magnesium stearate and microcrystalline cellulose. The white film-coating contains  
76 hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

77 The tablets are printed with red ink that includes FD&C Red #40 Aluminum Lake as the  
78 colorant. There is a large T printed on both sides of the tablet, as well as the word  
79 TORADOL on one side, and the word ROCHE on the other.

80 **CLINICAL PHARMACOLOGY**

81 **Pharmacodynamics**

82 Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits  
83 analgesic activity in animal models. The mechanism of action of ketorolac, like that of

84 other NSAIDs, is not completely understood but may be related to prostaglandin  
85 synthetase inhibition. The biological activity of ketorolac tromethamine is associated  
86 with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

87 The peak analgesic effect of TORADOL occurs within 2 to 3 hours and is not statistically  
88 significantly different over the recommended dosage range of TORADOL. The greatest  
89 difference between large and small doses of TORADOL is in the duration of analgesia.

## 90 **Pharmacokinetics**

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

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

94 The pharmacokinetics of ketorolac tromethamine, following IV and IM doses of  
95 ketorolac tromethamine and oral doses of TORADOL, are compared in **Table 1**. In  
96 adults, the extent of bioavailability following administration of the ORAL form of  
97 TORADOL and the IM form of ketorolac tromethamine was equal to that following an  
98 IV bolus.

### 99 **Linear Kinetics**

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

### 107 **Absorption**

108 TORADOL is 100% absorbed after oral administration (see **Table 1**). Oral administration  
109 of TORADOL after a high-fat meal resulted in decreased peak and delayed time-to-peak  
110 concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the  
111 extent of absorption.

### 112 **Distribution**

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

120 Ketorolac tromethamine is excreted in human milk (see **PRECAUTIONS: Nursing**  
121 **Mothers**).

## 122 Metabolism

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

## 126 Excretion

127 The principal route of elimination of ketorolac and its metabolites is renal. About 92% of  
128 a given dose is found in the urine, approximately 40% as metabolites and 60% as  
129 unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose  
130 study with 10 mg TORADOL (n=9) demonstrated that the S-enantiomer is cleared  
131 approximately two times faster than the R-enantiomer and that the clearance was  
132 independent of the route of administration. This means that the ratio of S/R plasma  
133 concentrations decreases with time after each dose. There is little or no inversion of the  
134 R- to S- form in humans. The clearance of the racemate in normal subjects, elderly  
135 individuals and in hepatically and renally impaired patients is outlined in **Table 2** (see  
136 **CLINICAL PHARMACOLOGY: Kinetics in Special Populations**).

137 The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours  
138 (SD  $\pm$  0.4) compared with 5 hours (SD  $\pm$  1.7) for the R-enantiomer. In other studies, the  
139 half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

## 140 Accumulation

141 Ketorolac tromethamine administered as an IV bolus every 6 hours for 5 days to healthy  
142 subjects (n=13), showed no significant difference in  $C_{max}$  on Day 1 and Day 5. Trough  
143 levels averaged 0.29  $\mu$ g/mL (SD  $\pm$  0.13) on Day 1 and 0.55  $\mu$ g/mL (SD  $\pm$  0.23) on Day 6.  
144 Steady state was approached after the fourth dose.

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

## 147 Kinetics in Special Populations

### 148 Geriatric Patients

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

### 154 Pediatric Patients

155 Limited information is available regarding the pharmacokinetics of dosing of ketorolac  
156 tromethamine in the pediatric population. Following a single intravenous bolus dose of  
157 0.5 mg/kg in 10 children 4 to 8 years old, the half-life was 5.8  $\pm$  1.6 hours, the average  
158 clearance was 0.042  $\pm$  0.01 L/hr/kg, the volume of distribution during the terminal phase  
159 ( $V_{\beta}$ ) was 0.34  $\pm$  0.12 L/kg and the volume of distribution at steady state ( $V_{ss}$ ) was  
160 0.26  $\pm$  0.08 L/kg. The volume of distribution and clearance of ketorolac in pediatric

161 patients was higher than those observed in adult subjects (see **Table 1**). There are no  
162 pharmacokinetic data available for administration of ketorolac tromethamine by the IM  
163 route in pediatric patients.

#### 164 Renal Insufficiency

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

169 In patients with renal disease, the  $AUC_{\infty}$  of each enantiomer increased by approximately  
170 100% compared with healthy volunteers. The volume of distribution doubles for the  
171 S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of  
172 distribution of ketorolac tromethamine implies an increase in unbound fraction.

173 The  $AUC_{\infty}$ -ratio of the ketorolac tromethamine enantiomers in healthy subjects and  
174 patients remained similar, indicating there was no selective excretion of either enantiomer  
175 in patients compared to healthy subjects (see **WARNINGS: Renal Effects**).

#### 176 Hepatic Insufficiency

177 There was no significant difference in estimates of half-life,  $AUC_{\infty}$  and  $C_{max}$  in 7 patients  
178 with liver disease compared to healthy volunteers (see **PRECAUTIONS: Hepatic Effect**  
179 and **Table 2**).

#### 180 Race

181 Pharmacokinetic differences due to race have not been identified.

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

Pharmacokinetic Parameters (units)	Oral*	Intramuscular†			Intravenous Bolus‡	
	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T <sub>max</sub> <sup>1</sup> (min)	44 ± 34	33 ± 21§	44 ± 29	33 ± 21§	1.1 ± 0.7§	2.9 ± 1.8
C <sub>max</sub> <sup>2</sup> (µg/mL) [single-dose]	0.87 ± 0.22	1.14 ± 0.32§	2.42 ± 0.68	4.55 ± 1.27§	2.47 ± 0.51§	4.65 ± 0.96
C <sub>max</sub> (µg/mL) [steady state qid]	1.05 ± 0.26§	1.56 ± 0.44§	3.11 ± 0.87§	N/A	3.09 ± 1.17§	6.85 ± 2.61
C <sub>min</sub> <sup>3</sup> (µg/mL) [steady state qid]	0.29 ± 0.07§	0.47 ± 0.13§	0.93 ± 0.26§	N/A	0.61 ± 0.21§	1.04 ± 0.35
C <sub>avg</sub> <sup>4</sup> (µg/mL) [steady state qid]	0.59 ± 0.20§	0.94 ± 0.29§	1.88 ± 0.59§	N/A	1.09 ± 0.30§	2.17 ± 0.59
Vβ <sup>5</sup> (L/kg)	————— 0.175 ± 0.039 —————				0.210 ± 0.044	

% Dose metabolized = <50

% Dose excreted in feces = 6

% Dose excreted in urine = 91

% Plasma protein binding = 99

\* 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

§ 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

|| Not applicable because 60 mg is only recommended as a single dose

<sup>1</sup>Time-to-peak plasma concentration

<sup>2</sup>Peak plasma concentration

<sup>3</sup>Trough plasma concentration

<sup>4</sup>Average plasma concentration

<sup>5</sup>Volume of distribution

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

Type of Subjects	Total Clearance [in L/h/kg] <sup>3</sup>		Terminal Half-life [in hours]	
	IM	ORAL	IM	ORAL
	Mean (range)	Mean (range)	Mean (range)	Mean (range)
Normal Subjects IM (n=54) mean age=32, range=18–60 Oral (n=77) mean age=32, range=20–60	0.023 (0.010–0.046)	0.025 (0.013–0.050)	5.3 (3.5–9.2)	5.3 (2.4–9.0)
Healthy Elderly Subjects IM (n=13), Oral (n=12) mean age=72, range=65–78	0.019 (0.013–0.034)	0.024 (0.018–0.034)	7.0 (4.7–8.6)	6.1 (4.3–7.6)
Patients with Hepatic Dysfunction IM and Oral (n=7) mean age=51, range=43–64	0.029 (0.013–0.066)	0.033 (0.019–0.051)	5.4 (2.2–6.9)	4.5 (1.6–7.6)
Patients with Renal Impairment IM (n=25), Oral (n=9) serum creatinine=1.9–5.0 mg/dL, mean age (IM)=54, range=35–71 mean age (Oral)=57, range=39–70	0.015 (0.005–0.043)	0.016 (0.007–0.052)	10.3 (5.9–19.2)	10.8 (3.4–18.9)
Renal Dialysis Patients IM and Oral (n=9) mean age=40, range=27–63	0.016 (0.003–0.036)	—	13.6 (8.0–39.1)	—

<sup>1</sup> Estimated from 30 mg single IM doses of ketorolac tromethamine

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

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

188 **IV Administration**

189 In normal adult subjects (n=37), the total clearance of 30 mg IV-administered ketorolac  
190 tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9)  
191 hours. (See **Kinetics in Special Populations** for use of IV dosing of ketorolac  
192 tromethamine in pediatric patients.)

193 **CLINICAL STUDIES**

194 **Adult Patients**

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

201 **Pediatric Patients**

202 There are no data available to support the use of TORADOL<sup>ORAL</sup> in pediatric patients.

203 **INDICATIONS AND USAGE**

204 Carefully consider the potential benefits and risks of TORADOL and other treatment  
205 options before deciding to use TORADOL. Use the lowest effective dose for the shortest  
206 duration consistent with individual patient treatment goals.

207 **Acute Pain in Adult Patients**

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

213 The total combined duration of use of TORADOL<sup>ORAL</sup> and ketorolac tromethamine is not  
214 to exceed 5 days of use because of the potential of increasing the frequency and severity  
215 of adverse reactions associated with the recommended doses (see **WARNINGS,**  
216 **PRECAUTIONS, DOSAGE AND ADMINISTRATION,** and **ADVERSE**  
217 **REACTIONS**). Patients should be switched to alternative analgesics as soon as possible,  
218 but TORADOL<sup>ORAL</sup> therapy is not to exceed 5 days.

219 **CONTRAINDICATIONS (see also Boxed WARNING)**

220 TORADOL is contraindicated in patients with previously demonstrated hypersensitivity  
221 to ketorolac tromethamine.

222 TORADOL is contraindicated in patients with active peptic ulcer disease, in patients with  
223 recent gastrointestinal bleeding or perforation and in patients with a history of peptic  
224 ulcer disease or gastrointestinal bleeding.

225 TORADOL should not be given to patients who have experienced asthma, urticaria, or  
226 allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal,  
227 anaphylactic-like reactions to NSAIDs have been reported in such patients (see  
228 **WARNINGS: Anaphylactoid Reactions**, and **PRECAUTIONS: Preexisting Asthma**).

229 TORADOL is contraindicated as prophylactic analgesic before any major surgery.

230 TORADOL is contraindicated for the treatment of peri-operative pain in the setting of  
231 coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

232 TORADOL is contraindicated in patients with advanced renal impairment or in patients  
233 at risk for renal failure due to volume depletion (see **WARNINGS** for correction of  
234 volume depletion).

235 TORADOL is contraindicated in labor and delivery because, through its prostaglandin  
236 synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine  
237 contractions, thus increasing the risk of uterine hemorrhage.

238 The use of TORADOL is contraindicated in nursing mothers because of the potential  
239 adverse effects of prostaglandin-inhibiting drugs on neonates.

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

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

245 The concomitant use of TORADOL and probenecid is contraindicated.

246 The concomitant use of ketorolac tromethamine and pentoxifylline is contraindicated.

#### 247 **WARNINGS (see also Boxed WARNING)**

248 The total combined duration of use of TORADOL<sup>ORAL</sup> and IV or IM dosing of ketorolac  
249 tromethamine is not to exceed 5 days in adults. TORADOL<sup>ORAL</sup> is not indicated for use  
250 in pediatric patients.

251 The most serious risks associated with TORADOL are:

#### 252 **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**

253 TORADOL is contraindicated in patients with previously documented peptic ulcers  
254 and/or GI bleeding. Toradol can cause serious gastrointestinal (GI) adverse events  
255 including bleeding, ulceration and perforation, of the stomach, small intestine, or large  
256 intestine, which can be fatal. These serious adverse events can occur at any time, with or  
257 without warning symptoms, in patients treated with TORADOL.

258 Only one in five patients who develop a serious upper GI adverse event on NSAID  
259 therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are  
260 common and may also occur at any time during NSAID therapy. The incidence and  
261 severity of gastrointestinal complications increases with increasing dose of, and duration

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

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

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

## 278 **Hemorrhage**

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

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

## 296 **Renal Effects**

297 Long-term administration of NSAIDs has resulted in renal papillary necrosis and other  
298 renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins  
299 have a compensatory role in the maintenance of renal perfusion. In these patients,  
300 administration of a NSAID may cause a dose-dependent reduction in prostaglandin  
301 formation and, secondarily, in renal blood flow, which may precipitate overt renal  
302 decompensation. Patients at greatest risk of this reaction are those with impaired renal  
303 function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and

304 the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the  
305 pretreatment state.

306 TORADOL and its metabolites are eliminated primarily by the kidneys, which, in  
307 patients with reduced creatinine clearance, will result in diminished clearance of the drug  
308 (see **CLINICAL PHARMACOLOGY**). Therefore, TORADOL should be used with  
309 caution in patients with impaired renal function (see **DOSAGE AND**  
310 **ADMINISTRATION**) and such patients should be followed closely. With the use of  
311 TORADOL, there have been reports of acute renal failure, interstitial nephritis and  
312 nephrotic syndrome.

### 313 **Impaired Renal Function**

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

### 321 **Anaphylactoid Reactions**

322 As with other NSAIDs, anaphylactoid reactions may occur in patients without a known  
323 previous exposure or hypersensitivity to TORADOL. TORADOL should not be given to  
324 patients with the aspirin triad. This symptom complex typically occurs in asthmatic  
325 patients who experience rhinitis with or without nasal polyps, or who exhibit severe,  
326 potentially fatal bronchospasm after taking aspirin or other NSAIDs (see  
327 **CONTRAINDICATIONS** and **PRECAUTIONS: Preexisting Asthma**). Anaphylactoid  
328 reactions, like anaphylaxis, may have a fatal outcome. Emergency help should be sought  
329 in cases where an anaphylactoid reaction occurs.

### 330 **Cardiovascular Effects**

#### 331 **Cardiovascular Thrombotic Events**

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

342 There is no consistent evidence that concurrent use of aspirin mitigates the increased risk  
343 of serious CV thrombotic events associated with NSAID use. The concurrent use of  
344 aspirin and an NSAID does increase the risk of serious GI events (see **Gastrointestinal**

345 **Effects – Risk of Ulceration, Bleeding, and Perforation**). Two large, controlled clinical  
346 trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days  
347 following CABG surgery found an increased incidence of myocardial infarction and  
348 stroke (see **CONTRAINDICATIONS**).

#### 349 Hypertension

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

#### 356 **Congestive Heart Failure and Edema**

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

#### 361 **Skin Reactions**

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

#### 368 **Pregnancy**

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

### 371 **PRECAUTIONS**

#### 372 **General**

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

377 The pharmacological activity of TORADOL in reducing inflammation may diminish the  
378 utility of this diagnostic sign in detecting complications of presumed noninfectious,  
379 painful conditions.

#### 380 **Hepatic Effect**

381 TORADOL should be used with caution in patients with impaired hepatic function or a  
382 history of liver disease. Borderline elevations of one or more liver tests may occur in up

383 to 15% of patients taking NSAIDs including TORADOL. These laboratory abnormalities  
384 may progress, may remain unchanged, or may be transient with continuing therapy.  
385 Notable elevations of ALT or AST (approximately three or more times the upper limit of  
386 normal) have been reported in approximately 1% of patients in clinical trials with  
387 NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal  
388 fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes  
389 have been reported.

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

### 395 Hematologic Effect

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

### 405 Preexisting Asthma

406 Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients  
407 with aspirin-sensitive asthma has been associated with severe bronchospasm which can  
408 be fatal. Since cross reactivity, including bronchospasm, between aspirin and other  
409 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients,  
410 TORADOL should not be administered to patients with this form of aspirin sensitivity  
411 and should be used with caution in patients with preexisting asthma.

### 412 Information for Patients

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

415 Physicians, when prescribing TORADOL, should inform their patients or their guardians  
416 of the potential risks of TORADOL treatment (see **Boxed WARNING, WARNINGS,**  
417 **PRECAUTIONS,** and **ADVERSE REACTIONS** sections), instruct patients to seek  
418 medical advice if they develop treatment-related adverse events, and **advise patients not**  
419 **to give TORADOL<sup>ORAL</sup> to other family members and to discard any unused drug.**

420 Remember that the total combined duration of use of TORADOL<sup>ORAL</sup> and IV or IM  
421 dosing of ketorolac tromethamine is not to exceed 5 days in adults. TORADOL<sup>ORAL</sup> is  
422 not indicated for use in pediatric patients.

423 Patients should be informed of the following information before initiating therapy with an  
424 NSAID and periodically during the course of ongoing therapy. Patients should also be  
425 encouraged to read the NSAID Medication Guide that accompanies each prescription  
426 dispensed.

- 427 1. TORADOL, like other NSAIDs, may cause serious CV side effects, such as MI or  
428 stroke, which may result in hospitalization and even death. Although serious CV  
429 events can occur without warning symptoms, patients should be alert for the signs and  
430 symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should  
431 ask for medical advice when observing any indicative sign or symptoms. Patients  
432 should be apprised of the importance of this follow-up (see **WARNINGS:**  
433 **Cardiovascular Effects**).
- 434 2. TORADOL, like other NSAIDs, can cause GI discomfort and rarely, serious GI side  
435 effects, such as ulcers and bleeding, which may result in hospitalization and even  
436 death. Although serious GI tract ulcerations and bleeding can occur without warning  
437 symptoms, patients should be alert for the signs and symptoms of ulcerations and  
438 bleeding, and should ask for medical advice when observing any indicative sign or  
439 symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients  
440 should be apprised of the importance of this follow-up (see **WARNINGS:**  
441 **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**).
- 442 3. TORADOL, like other NSAIDs, can cause serious skin side effects such as  
443 exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even  
444 death. Although serious skin reactions may occur without warning, patients should be  
445 alert for the signs and symptoms of skin rash and blisters, fever, or other signs of  
446 hypersensitivity such as itching, and should ask for medical advice when observing  
447 any indicative signs or symptoms. Patients should be advised to stop the drug  
448 immediately if they develop any type of rash and contact their physicians as soon as  
449 possible.
- 450 4. Patients should promptly report signs or symptoms of unexplained weight gain or  
451 edema to their physicians.
- 452 5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (eg,  
453 nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-  
454 like” symptoms). If these occur, patients should be instructed to stop therapy and seek  
455 immediate medical therapy.
- 456 6. Patients should be informed of the signs of an anaphylactoid reaction (eg, difficulty  
457 breathing, swelling of the face or throat). If these occur, patients should be instructed  
458 to seek immediate emergency help (see **WARNINGS**).
- 459 7. In late pregnancy, as with other NSAIDs, TORADOL should be avoided because it  
460 will cause premature closure of the ductus arteriosus.

#### 461 **Laboratory Tests**

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

468 **Drug Interactions**

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

472 **Warfarin, Digoxin, Salicylate, and Heparin**

473 The in vitro binding of *warfarin* to plasma proteins is only slightly reduced by ketorolac  
474 tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to  
475 10 µg/mL. Ketorolac does not alter *digoxin* protein binding. In vitro studies indicate that,  
476 at therapeutic concentrations of *salicylate* (300 µg/mL), the binding of ketorolac was  
477 reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in  
478 unbound ketorolac plasma levels. Therapeutic concentrations of *digoxin*, *warfarin*,  
479 *ibuprofen*, *naproxen*, *piroxicam*, *acetaminophen*, *phenytoin* and *tolbutamide* did not  
480 alter ketorolac tromethamine protein binding.

481 In a study involving 12 adult volunteers, TORADOL<sup>ORAL</sup> was coadministered with a  
482 single dose of 25 mg *warfarin*, causing no significant changes in pharmacokinetics or  
483 pharmacodynamics of warfarin. In another study, ketorolac tromethamine dosed IV or IM  
484 was given with two doses of 5000 U of *heparin* to 11 healthy volunteers, resulting in a  
485 mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6.0  
486 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo.  
487 Although these results do not indicate a significant interaction between TORADOL and  
488 warfarin or heparin, the administration of TORADOL to patients taking anticoagulants  
489 should be done extremely cautiously, and patients should be closely monitored (see  
490 **WARNINGS** and **PRECAUTIONS: Hematologic Effect**).

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

494 **Aspirin**

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

500 **Diuretics**

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

506 Probenecid

507 Concomitant administration of TORADOL<sup>ORAL</sup> and *probenecid* resulted in decreased  
508 clearance and volume of distribution of ketorolac and significant increases in ketorolac  
509 plasma levels (total AUC increased approximately threefold from 5.4 to 17.8 µg/h/mL)  
510 and terminal half-life increased approximately twofold from 6.6 to 15.1 hours. Therefore,  
511 concomitant use of TORADOL and probenecid is contraindicated.

512 Lithium

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

519 Methotrexate

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

524 ACE Inhibitors/Angiotension II Receptor Antagonists

525 Concomitant use of *ACE inhibitors and/or angiotension II receptor antagonists* may  
526 increase the risk of renal impairment, particularly in volume-depleted patients.

527 Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors  
528 and/or angiotension II receptor antagonists. This interaction should be given  
529 consideration in patients taking NSAIDs concomitantly with ACE inhibitors and/or  
530 angiotension II receptor antagonists.

531 Antiepileptic Drugs

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

534 Psychoactive Drugs

535 Hallucinations have been reported when TORADOL was used in patients taking  
536 *psychoactive drugs* (fluoxetine, thiothixene, alprazolam).

537 Pentoxifylline

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

540 Nondepolarizing Muscle Relaxants

541 In postmarketing experience there have been reports of a possible interaction between  
542 ketorolac tromethamine<sup>IV/IM</sup> and *nondepolarizing muscle relaxants* that resulted in

543 apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been  
544 formally studied.

#### 545 Selective Serotonin Reuptake Inhibitors (SSRIs)

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

#### 549 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

550 An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day  
551 (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg qid,  
552 based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in  
553 rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity.

554 Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA  
555 synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not  
556 cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 µg/mL  
557 and at higher concentrations, ketorolac tromethamine increased the incidence of  
558 chromosomal aberrations in Chinese hamster ovarian cells.

559 Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg  
560 (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac  
561 tromethamine, respectively.

#### 562 **Pregnancy**

##### 563 **Teratogenic Effects: Pregnancy Category C**

564 Reproduction studies have been performed during organogenesis using daily oral doses  
565 of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at  
566 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal  
567 evidence of teratogenicity to the fetus. However, animal reproduction studies are not  
568 always predictive of human response.

##### 569 **Nonteratogenic Effects**

570 Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal  
571 cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly  
572 late pregnancy) should be avoided. Oral doses of ketorolac tromethamine at 1.5 mg/kg  
573 (0.14 times the human AUC), administered after gestation Day 17, caused dystocia and  
574 higher pup mortality in rats.

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

##### 578 **Labor and Delivery**

579 The use of TORADOL is contraindicated in labor and delivery because, through its  
580 prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and

581 inhibit uterine contractions, thus increasing the risk of uterine hemorrhage (see  
582 **CONTRAINDICATIONS**).

### 583 Effects on Fertility

584 The use of ketorolac tromethamine, as with any drug known to inhibit  
585 cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in  
586 women attempting to conceive. In women who have difficulty conceiving or are  
587 undergoing investigation of infertility, withdrawal of ketorolac tromethamine should be  
588 considered.

### 589 Nursing Mothers

590 After a single administration of 10 mg of TORADOL<sup>ORAL</sup> to humans, the maximum milk  
591 concentration observed was 7.3 ng/mL, and the maximum milk-to-plasma ratio was  
592 0.037. After 1 day of dosing (qid), the maximum milk concentration was 7.9 ng/mL, and  
593 the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of  
594 prostaglandin-inhibiting drugs on neonates, use in nursing mothers is contraindicated.

### 595 Pediatric Use

596 TORADOL<sup>ORAL</sup> is not indicated for use in pediatric patients. The safety and effectiveness  
597 of TORADOL<sup>ORAL</sup> in pediatric patients below the age of 17 have not been established.

### 598 Geriatric Use (≥65 years of age)

599 Because ketorolac tromethamine may be cleared more slowly by the elderly (see  
600 **CLINICAL PHARMACOLOGY**) who are also more sensitive to the dose-related  
601 adverse effects of NSAIDs (see **WARNINGS: Gastrointestinal Effects – Risk of  
602 Ulceration, Bleeding, and Perforation**), extreme caution, reduced dosages (see  
603 **DOSAGE AND ADMINISTRATION**), and careful clinical monitoring must be used  
604 when treating the elderly with TORADOL.

### 605 ADVERSE REACTIONS

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

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

Gastrointestinal (GI) experiences including:

abdominal pain*	constipation/diarrhea	dyspepsia*
flatulence	GI fullness	GI ulcers (gastric/duodenal)

gross bleeding/perforation	Heartburn	nausea*
stomatitis	Vomiting	
Other experiences:		
abnormal renal function	Anemia	dizziness
drowsiness	Edema	elevated liver enzymes
headaches*	Hypertension	increased bleeding time
injection site pain	Pruritus	purpura
rashes	Tinnitus	sweating

\*Incidence greater than 10%

615

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

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

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

620 **Dermatologic:** alopecia, photosensitivity, urticaria

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

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

625 **Metabolic and Nutritional:** weight change

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

630 **Reproductive, female:** infertility

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

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

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

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

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

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

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

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

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

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

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

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

651 **Special Senses:** conjunctivitis

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

#### 654 **Postmarketing Surveillance Study**

655 A large postmarketing observational, nonrandomized study, involving approximately  
656 10,000 patients receiving ketorolac tromethamine<sup>IV/IM</sup>, demonstrated that the risk of  
657 clinically serious gastrointestinal (GI) bleeding was dose-dependent (see Tables 3A and  
658 3B). This was particularly true in elderly patients who received an average daily dose  
659 greater than 60 mg/day of ketorolac tromethamine<sup>IV/IM</sup> (see Table 3A).

660 **Table 3** Incidence of Clinically Serious GI Bleeding as Related to  
661 Age, Total Daily Dose, and History of GI Perforation, Ulcer,  
662 Bleeding (PUB) After up to 5 Days of Treatment With  
663 Ketorolac Tromethamine<sup>IV/IM</sup>

664 **A. Adult Patients Without History of PUB**

Age of Patients	Total Daily Dose of Ketorolac Tromethamine <sup>IV/IM</sup>			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

665 **B. Adult Patients With History of PUB**

Age of Patients	Total Daily Dose of Ketorolac Tromethamine <sup>IV/IM</sup>			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25.0%

666

667 **OVERDOSAGE**

668 **Symptoms and Signs**

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

675 **Treatment**

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

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

685 **DOSAGE AND ADMINISTRATION**

686 Carefully consider the potential benefits and risks of TORADOL and other  
687 treatment options before deciding to use TORADOL. Use the lowest effective dose  
688 for the shortest duration consistent with individual patient treatment goals. In  
689 adults, the combined duration of use of IV or IM dosing of ketorolac tromethamine  
690 and TORADOL<sup>ORAL</sup> is not to exceed 5 days. In adults, the use of TORADOL<sup>ORAL</sup> is

691 **only indicated as continuation therapy to IV or IM dosing of ketorolac**  
692 **tromethamine.**

693 **Transition from IV or IM dosing of ketorolac tromethamine (single- or multiple-**  
694 **dose) to multiple-dose TORADOL<sup>ORAL</sup>:**

695 Patients age 17 to 64: 20 mg PO once followed by 10 mg q4-6 hours prn **not >40 mg/day**

696 Patients age  $\geq 65$ , renally impaired, and/or weight <50 kg (110 lbs): 10 mg PO once  
697 followed by 10 mg q4-6 hours prn **not >40 mg/day**

698 **Note:**

699 **Oral formulation should not be given as an initial dose**

700 **Use minimum effective dose** for the individual patient

701 **Do not shorten dosing interval** of 4 to 6 hours

702 **Total duration of treatment in adult patients:** the combined duration of use of IV or  
703 IM dosing of ketorolac tromethamine and TORADOL<sup>ORAL</sup> is not to exceed 5 days.

704 The following table summarizes TORADOL<sup>ORAL</sup> dosing instructions in terms of age  
705 group:

706 **Table 4 Summary of Dosing Instructions**

<b>Patient Population</b>	<b>TORADOL<sup>ORAL</sup> (following IV or IM dosing of ketorolac tromethamine)</b>
Age <17 years	Oral not approved
Adult Age 17 to 64 years	20 mg once, then 10 mg q4-6 hours prn not >40 mg/day
Adult Age $\geq 65$ years, renally impaired, and/or weight <50 kg	10 mg once, then 10 mg q4-6 hours prn not >40 mg/day

707

708 **HOW SUPPLIED**

709 **TORADOL<sup>ORAL</sup>** 10 mg tablets are round, white, film-coated, red printed tablets. There is  
710 a large T printed on both sides of the tablet, with TORADOL on one side, and ROCHE  
711 on the other, available in bottles of 100 tablets (NDC 0004-0273-01).

712 **Storage**

713 Store bottles at 15° to 30°C (59° to 86°F).

714 **MEDICATION GUIDE FOR NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**  
715 **(NSAIDS)**

716 (See the end of this Medication Guide  
717 for a list of prescription NSAID medicines.)

718 **What is the most important information I should know about medicines called**  
719 **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?**

720 **NSAID medicines may increase the chance of a heart attack or stroke that can lead**  
721 **to death.** This chance increases:

- 722 • with longer use of NSAID medicines  
723 • in people who have heart disease

724  
725 **NSAID medicines should never be used right before or after a heart surgery called a**  
726 **“coronary artery bypass graft (CABG).”**

727 **NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any**  
728 **time during treatment. Ulcers and bleeding:**

- 729 • can happen without warning symptoms  
730 • may cause death

731  
732 **The chance of a person getting an ulcer or bleeding increases with:**

- 733 • taking medicines called “corticosteroids” and “anticoagulants”  
734 • longer use  
735 • smoking  
736 • drinking alcohol  
737 • older age  
738 • having poor health

739  
740 **NSAID medicines should only be used:**

- 741 • exactly as prescribed  
742 • at the lowest dose possible for your treatment  
743 • for the shortest time needed

744  
745 **What are Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?**

746 NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation)  
747 from medical conditions such as:

- 748 • different types of arthritis  
749 • menstrual cramps and other types of short-term pain

750  
751 **Who should not take a Nonsteroidal Anti-Inflammatory Drug (NSAID)?**

752 **Do not take an NSAID medicine:**

- 753 • if you had an asthma attack, hives, or other allergic reaction with aspirin or any other  
754 NSAID medicine  
755 • for pain right before or after heart bypass surgery  
756

757 **Tell your healthcare provider:**

- 758 • about all of your medical conditions.  
759 • about all of the medicines you take. NSAIDs and some other medicines can interact  
760 with each other and cause serious side effects. **Keep a list of your medicines to show**  
761 **to your healthcare provider and pharmacist.**  
762 • if you are pregnant. **NSAID medicines should not be used by pregnant women late**  
763 **in their pregnancy.**  
764 • if you are breastfeeding. Talk to your doctor.  
765

766 **What are the possible side effects of Nonsteroidal Anti-Inflammatory Drugs**  
767 **(NSAIDs)?**

<b>Serious side effects include:</b>	<b>Other side effects include:</b>
<ul style="list-style-type: none"><li>• heart attack</li><li>• stroke</li><li>• high blood pressure</li><li>• heart failure from body swelling (fluid retention)</li><li>• kidney problems including kidney failure</li><li>• bleeding and ulcers in the stomach and intestine</li><li>• low red blood cells (anemia)</li><li>• life-threatening skin reactions</li><li>• life-threatening allergic reactions</li><li>• liver problems including liver failure</li><li>• asthma attacks in people who have asthma</li></ul>	<ul style="list-style-type: none"><li>• stomach pain</li><li>• constipation</li><li>• diarrhea</li><li>• gas</li><li>• heartburn</li><li>• nausea</li><li>• vomiting</li><li>• dizziness</li></ul>

768  
769 **Get emergency help right away if you have any of the following symptoms:**

- 770 • shortness of breath or trouble breathing  
771 • chest pain  
772 • weakness in one part or side of your body  
773 • slurred speech  
774 • swelling of the face or throat  
775

776 **Stop your NSAID medicine and call your healthcare provider right away if you have**  
777 **any of the following symptoms:**

- 778 • nausea  
779 • more tired or weaker than usual  
780 • itching  
781 • your skin or eyes look yellow

- 782 • stomach pain
- 783 • flu-like symptoms
- 784 • vomit blood
- 785 • there is blood in your bowel movement or it is black and sticky like tar
- 786 • unusual weight gain
- 787 • skin rash or blisters with fever
- 788 • swelling of the arms and legs, hands and feet

789

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

792 **Other information about Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):**

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

799

800 **NSAID medicines that need a prescription:**

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic

Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

801 \*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used  
802 for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may  
803 increase the risk of heart attack or stroke.  
804

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

806 Date created: June 15, 2005

807

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