



TORADOL® 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**).

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### 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**).

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

### RISK DURING LABOR AND DELIVERY

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

### CONCOMITANT USE WITH NSAIDs

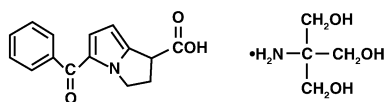
- TORADOL is CONTRAINDICATED in patients currently receiving aspirin or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

### 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**).

### DESCRIPTION

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



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

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

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

### 81 **CLINICAL PHARMACOLOGY**

#### 82 **Pharmacodynamics**

83 Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits  
84 analgesic activity in animal models. The mechanism of action of ketorolac, like that of  
85 other NSAIDs, is not completely understood but may be related to prostaglandin  
86 synthetase inhibition. The biological activity of ketorolac tromethamine is associated  
87 with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

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

#### 91 **Pharmacokinetics**

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

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

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

#### 100 **Linear Kinetics**

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

#### 108 **Absorption**

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

#### 113 **Distribution**

114 The mean apparent volume ( $V\beta$ ) of ketorolac tromethamine following complete  
115 distribution was approximately 13 liters. This parameter was determined from single-

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116 dose data. The ketorolac tromethamine racemate has been shown to be highly protein  
117 bound (99%). Nevertheless, plasma concentrations as high as 10 µg/mL will only occupy  
118 approximately 5% of the albumin binding sites. Thus, the unbound fraction for each  
119 enantiomer will be constant over the therapeutic range. A decrease in serum albumin,  
120 however, will result in increased free drug concentrations.

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

### 123 Metabolism

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

### 127 Excretion

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

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

### 141 Accumulation

142 Ketorolac tromethamine administered as an IV bolus every 6 hours for 5 days to healthy  
143 subjects (n=13), showed no significant difference in C<sub>max</sub> on Day 1 and Day 5. Trough  
144 levels averaged 0.29 µg/mL (SD ± 0.13) on Day 1 and 0.55 µg/mL (SD ± 0.23) on Day 6.  
145 Steady state was approached after the fourth dose.

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

### 148 Kinetics in Special Populations

#### 149 Geriatric Patients

150 Based on single-dose data only, the half-life of the ketorolac tromethamine racemate  
151 increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy  
152 volunteers (24 to 35 years) (see **Table 2**). There was little difference in the C<sub>max</sub> for the  
153 two groups (elderly, 2.52 µg/mL ± 0.77; young, 2.99 µg/mL ± 1.03) (see  
154 **PRECAUTIONS: Geriatric Use**).

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### 155 Pediatric Patients

156 Limited information is available regarding the pharmacokinetics of dosing of ketorolac  
157 tromethamine in the pediatric population. Following a single intravenous bolus dose of  
158 0.5 mg/kg in 10 children 4 to 8 years old, the half-life was  $5.8 \pm 1.6$  hours, the average  
159 clearance was  $0.042 \pm 0.01$  L/hr/kg, the volume of distribution during the terminal phase  
160 ( $V_{\beta}$ ) was  $0.34 \pm 0.12$  L/kg and the volume of distribution at steady state ( $V_{ss}$ ) was  
161  $0.26 \pm 0.08$  L/kg. The volume of distribution and clearance of ketorolac in pediatric  
162 patients was higher than those observed in adult subjects (see **Table 1**). There are no  
163 pharmacokinetic data available for administration of ketorolac tromethamine by the IM  
164 route in pediatric patients.

### 165 Renal Insufficiency

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

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

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

### 177 Hepatic Insufficiency

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

### 181 Race

182 Pharmacokinetic differences due to race have not been identified.

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**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

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**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

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### 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

#### 202 **Pediatric Patients**

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

### 204 **INDICATIONS AND USAGE**

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

#### 208 **Acute Pain in Adult Patients**

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

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

### 220 **CONTRAINDICATIONS (SEE ALSO BOXED WARNING)**

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

223



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

227 TORADOL should not be given to patients who have experienced asthma, urticaria, or  
228 allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal,  
229 anaphylactic-like reactions to NSAIDs have been reported in such patients (see  
230 **WARNINGS:**

231 **Anaphylactoid Reactions, and PRECAUTIONS: Preexisting Asthma).**

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

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

235

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

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

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

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

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

249 The concomitant use of TORADOL and probenecid is contraindicated.

250 **The concomitant use of ketorolac tromethamine and pentoxifylline is contraindicated .**

### 251 **WARNINGS (SEE ALSO BOXED WARNING)**

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

255 The most serious risks associated with TORADOL are:

### 256 **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and** 257 **Perforation**

258 TORADOL is contraindicated in patients with previously documented peptic ulcers  
259 and/or GI bleeding. Toradol can cause serious gastrointestinal (GI) adverse events

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260 including bleeding, ulceration and perforation, of the stomach, small intestine, or large  
261 intestine, which can be fatal. These serious adverse events can occur at any time, with or  
262 without warning symptoms, in patients treated with TORADOL.

263 Only one in five patients who develop a serious upper GI adverse event on NSAID  
264 therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are  
265 common and may also occur at any time during NSAID therapy. The incidence and  
266 severity of gastrointestinal complications increases with increasing dose of, and duration  
267 of treatment with, TORADOL. Do not use TORADOL for more than five days.  
268 However, even short-term therapy is not without risk. In addition to past history of ulcer  
269 disease, other factors that increase the risk for GI bleeding in patients treated with  
270 NSAIDs include concomitant use of oral corticosteroids, or anticoagulants, longer  
271 duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health  
272 status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients  
273 and therefore, special care should be taken in treating this population.

274

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

282

### 283 Hemorrhage

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

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

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### 301 **Renal Effects**

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

311

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

### 319 **Impaired Renal Function**

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

### 327 **Anaphylactoid Reactions**

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

### 336 **Cardiovascular Effects**

#### 337 **Cardiovascular Thrombotic Events**

338 Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years  
339 duration have shown an increased risk of serious cardiovascular (CV) thrombotic events,  
340 myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective

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341 and nonselective, may have a similar risk. Patients with known CV disease or risk factors  
342 for CV disease may be at greater risk. To minimize the potential risk for an adverse CV  
343 event in patients treated with an NSAID, the lowest effective dose should be used for the  
344 shortest duration possible. Physicians and patients should remain alert for the  
345 development of such events, even in the absence of previous CV symptoms. Patients  
346 should be informed about the signs and/or symptoms of serious CV events and the steps  
347 to take if they occur.

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

### 355 Hypertension

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

### 362 Congestive Heart Failure and Edema

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

### 367 Skin Reactions

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

### 374 Pregnancy

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

377 **PRECAUTIONS**

378 **General**

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

383 The pharmacological activity of TORADOL in reducing inflammation may diminish the  
384 utility of this diagnostic sign in detecting complications of presumed noninfectious,  
385 painful conditions.

386 **Hepatic Effect**

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

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

401 **Hematologic Effect**

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

411 **Preexisting Asthma**

412 Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients  
413 with aspirin-sensitive asthma has been associated with severe bronchospasm which can  
414 be fatal. Since cross reactivity, including bronchospasm, between aspirin and other  
415 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients,

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416 TORADOL should not be administered to patients with this form of aspirin sensitivity  
417 and should be used with caution in patients with preexisting asthma.

### 418 Information for Patients

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

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

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

429 Patients should be informed of the following information before initiating therapy with an  
430 NSAID and periodically during the course of ongoing therapy. Patients should also be  
431 encouraged to read the NSAID Medication Guide that accompanies each prescription  
432 dispensed.

- 433 1. TORADOL, like other NSAIDs, may cause serious CV side effects, such as MI or  
434 stroke, which may result in hospitalization and even death. Although serious CV  
435 events can occur without warning symptoms, patients should be alert for the signs and  
436 symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should  
437 ask for medical advice when observing any indicative sign or symptoms. Patients  
438 should be apprised of the importance of this follow-up (see **WARNINGS:**  
439 **Cardiovascular Effects**).
- 440 2. TORADOL, like other NSAIDs, can cause GI discomfort and rarely, serious GI side  
441 effects, such as ulcers and bleeding, which may result in hospitalization and even  
442 death. Although serious GI tract ulcerations and bleeding can occur without warning  
443 symptoms, patients should be alert for the signs and symptoms of ulcerations and  
444 bleeding, and should ask for medical advice when observing any indicative sign or  
445 symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients  
446 should be apprised of the importance of this follow-up (see **WARNINGS,**  
447 **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**).
- 448 3. TORADOL, like other NSAIDs, can cause serious skin side effects such as  
449 exfoliative dermatitis, SJS, and TEN, which may results in hospitalizations and even  
450 death. Although serious skin reactions may occur without warning, patients should be  
451 alert for the signs and symptoms of skin rash and blisters, fever, or other signs of  
452 hypersensitivity such as itching, and should ask for medical advice when observing  
453 any indicative signs or symptoms. Patients should be advised to stop the drug  
454 immediately if they develop any type of rash and contact their physicians as soon as  
455 possible.
- 456 4. Patients should promptly report signs or symptoms of unexplained weight gain or  
457 edema to their physicians.

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- 458 5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (eg,  
459 nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-  
460 like” symptoms). If these occur, patients should be instructed to stop therapy and seek  
461 immediate medical therapy.
- 462 6. Patients should be informed of the signs of an anaphylactoid reaction (eg, difficulty  
463 breathing, swelling of the face or throat). If these occur, patients should be instructed  
464 to seek immediate emergency help (see **WARNINGS**).
- 465 7. In late pregnancy, as with other NSAIDs, TORADOL should be avoided because it  
466 will cause premature closure of the ductus arteriosus.

### 467 **Laboratory Tests**

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

### 474 **Drug Interactions**

475 Ketorolac is highly bound to human plasma protein (mean 99.2%). There is no evidence  
476 in animal or human studies that TORADOL induces or inhibits hepatic enzymes capable  
477 of metabolizing itself or other drugs.  
478

#### 479 Warfarin, Digoxin, Salicylate, and Heparin

480 The in vitro binding of *warfarin* to plasma proteins is only slightly reduced by ketorolac  
481 tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to  
482 10 µg/mL. Ketorolac does not alter *digoxin* protein binding. In vitro studies indicate that,  
483 at therapeutic concentrations of *salicylate* (300 µg/mL), the binding of ketorolac was  
484 reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in  
485 unbound ketorolac plasma levels. Therapeutic concentrations of *digoxin*, *warfarin*,  
486 *ibuprofen*, *naproxen*, *piroxicam*, *acetaminophen*, *phenytoin* and *tolbutamide* did not  
487 alter ketorolac tromethamine protein binding.

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

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

### 501 Aspirin

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

### 507 Diuretics

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

### 513 Probenecid

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

### 519 Lithium

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

### 526 Methotrexate

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

### 531 ACE Inhibitors

532 Concomitant use of *ACE inhibitors* may increase the risk of renal impairment,  
533 particularly in volume-depleted patients.



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534 Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-  
535 inhibitors. This interaction should be given consideration in patients taking NSAIDs  
536 concomitantly with ACE-inhibitors.

### 537 Antiepileptic Drugs

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

### 540 Psychoactive Drugs

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

### 543 Pentoxifylline

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

### 546 Nondepolarizing Muscle Relaxants (yes)

547 In postmarketing experience there have been reports of a possible interaction between  
548 ketorolac tromethamine<sup>IV/IM</sup> and *nondepolarizing muscle relaxants* that resulted in  
549 apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been  
550 formally studied.

551

## 552 Carcinogenesis, Mutagenesis and Impairment of Fertility

553 An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day  
554 (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg qid,  
555 based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in  
556 rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity.

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

562 Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg  
563 (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac  
564 tromethamine, respectively.

## 565 Pregnancy

### 566 Teratogenic Effects: Pregnancy Category C

567 Reproduction studies have been performed during organogenesis using daily oral doses  
568 of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at  
569 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal

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570 evidence of teratogenicity to the fetus. However, animal reproduction studies are not  
571 always predictive of human response.

### 572 **Nonteratogenic Effects**

573 Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal  
574 cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly  
575 late pregnancy) should be avoided. Oral doses of ketorolac tromethamine at 1.5 mg/kg  
576 (0.14 times the human AUC), administered after gestation Day 17, caused dystocia and  
577 higher pup mortality in rats.

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

### 581 **Labor and Delivery**

582 The use of TORADOL is contraindicated in labor and delivery because, through its  
583 prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and  
584 inhibit uterine contractions, thus increasing the risk of uterine hemorrhage (see  
585 **CONTRAINDICATIONS**).

#### 586 *Effects on Fertility:*

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

### 592 **Nursing Mothers**

593 After a single administration of 10 mg of TORADOL<sup>ORAL</sup> to humans, the maximum milk  
594 concentration observed was 7.3 ng/mL, and the maximum milk-to-plasma ratio was  
595 0.037. After 1 day of dosing (qid), the maximum milk concentration was 7.9 ng/mL, and  
596 the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of  
597 prostaglandin-inhibiting drugs on neonates, use in nursing mothers is contraindicated.

### 598 **Pediatric Use**

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

601

### 602 **Geriatric Use (≥65 years of age)**

603 Because ketorolac tromethamine may be cleared more slowly by the elderly (see  
604 **CLINICAL PHARMACOLOGY**) who are also more sensitive to the dose-related  
605 adverse effects of NSAIDs (see **WARNINGS: Gastrointestinal Effects – Risk of**  
606 **Ulceration, Bleeding, and Perforation**), extreme caution, reduced dosages (see

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607 **DOSAGE AND ADMINISTRATION**), and careful clinical monitoring must be used  
608 when treating the elderly with TORADOL.

### 609 **ADVERSE REACTIONS**

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

617 In patients taking TORADOL or other NSAIDs in clinical trials, the most frequently  
618 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%

619

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

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

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

624 **Dermatologic:** alopecia, photosensitivity, urticaria

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

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

629 **Metabolic and Nutritional:** weight change

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

634 Reproductive, female: infertility

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

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

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

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

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

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

645 **Dermatologic:** exfoliative dermatitis, erythema multiforme, Lyell's syndrome, Stevens-  
646 Johnson syndrome, toxic epidermal necrosis

647 **Gastrointestinal:** acute pancreatitis, liver failure

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

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

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

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

654 **Special Senses:** conjunctivitis

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

### 657 **Postmarketing Surveillance Study**

658 A large postmarketing observational, nonrandomized study, involving approximately  
659 10,000 patients receiving ketorolac tromethamine<sup>IV/IM</sup>, demonstrated that the risk of  
660 clinically serious gastrointestinal (GI) bleeding was dose-dependent (see Tables 3A and

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661 3B). This was particularly true in elderly patients who received an average daily dose  
662 greater than 60 mg/day of ketorolac tromethamine<sup>IV/IM</sup> (see Table 3A).

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

### 666 **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%

### 667 **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%

668  
669

## 670 **OVERDOSAGE**

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

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

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

## 686 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

699 **Note:**

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

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

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

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

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

707 **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 ≥65 years, renally impaired, and/or weight <50 kg	10 mg once, then 10 mg q4-6 hours prn not >40 mg/day

708

709 **HOW SUPPLIED**

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

713 **Storage**

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

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

715  
716  
717 (See the end of this Medication Guide  
718 for a list of prescription NSAID medicines.)

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

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

- 723 • with longer use of NSAID medicines  
724 • in people who have heart disease  
725

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

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

- 730 • can happen without warning symptoms  
731 • may cause death  
732

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

- 734 • taking medicines called “corticosteroids” and “anticoagulants”  
735 • longer use  
736 • smoking  
737 • drinking alcohol  
738 • older age  
739 • having poor health  
740

741 **NSAID medicines should only be used:**

- 742 • exactly as prescribed  
743 • at the lowest dose possible for your treatment  
744 • for the shortest time needed  
745

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

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

- 749 • different types of arthritis  
750 • menstrual cramps and other types of short-term pain  
751

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

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

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- 754 • if you had an asthma attack, hives, or other allergic reaction with aspirin or any other  
755 NSAID medicine
- 756 • for pain right before or after heart bypass surgery  
757

758 **Tell your healthcare provider:**

- 759 • about all of your medical conditions.
- 760 • about all of the medicines you take. NSAIDs and some other medicines can interact  
761 with each other and cause serious side effects. **Keep a list of your medicines to show**  
762 **to your healthcare provider and pharmacist.**
- 763 • if you are pregnant. **NSAID medicines should not be used by pregnant women late**  
764 **in their pregnancy.**
- 765 • if you are breastfeeding. Talk to your doctor.  
766

767 **What are the possible side effects of Nonsteroidal Anti-Inflammatory Drugs**  
768 **(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>

769

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

- 771 • shortness of breath or trouble breathing
- 772 • chest pain
- 773 • weakness in one part or side of your body
- 774 • slurred speech
- 775 • swelling of the face or throat  
776

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

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



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

790

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

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

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

800

### **801 NSAID medicines that need a prescription:**

<b>Generic Name</b>	<b>Tradename</b>
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

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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

802 \*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used  
803 for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may  
804 increase the risk of heart attack or stroke.  
805

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

807 Date created: June 15, 2005

808

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