



1

2

TORADOL® ORAL

3

(ketorolac tromethamine tablets)

4 **R_x only**

5 **WARNING**

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

12

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

17

18 **GASTROINTESTINAL RISK**

19 ■ Kеторолак трометамин, включая **TORADOL**, может вызвать язвы желудка и кишечника, гастроинтестинальное кровотечение и/или пр�орация желудка или кишечника, что может быть смертельным. Эти события могут произойти в любое время во время приема и без предупреждающих симптомов. Поэтому **TORADOL** противопоказан в случаях активной язвенной болезни, в случаях недавшегося гастроинтестинального кровотечения или пр�орации, а также у пациентов с историей язвенной болезни или гастроинтестинального кровотечения. Пожилые пациенты находятся в большем риске развития серьезных гастроинтестинальных событий (см. **WARNINGS**).

20

21 **CARDIOVASCULAR RISK**

22 ■ НСАИДы могут вызвать повышенный риск серьезных кардиоваскулярных тромботических событий, инфаркта миокарда и инсульта, что может быть смертельным. Этот риск может увеличиваться с продолжительностью приема. Пациенты с кардиоваскулярной болезнью или факторами риска кардиоваскулярной болезни могут находиться в большем риске. (См. **WARNINGS** и **CLINICAL TRIALS**).
23
24 ■ **TORADOL** противопоказан для лечения пери-оперативной боли в контексте коронарной артериальной бypass операции (CABG) (см. **WARNINGS**).
25

26

27 **RENAL RISK**

28 ■ **TORADOL** противопоказан в случаях выраженной почечной недостаточности и у пациентов с риском почечной недостаточности вследствие объемного дефицита (см. **WARNINGS**).
29
30
31
32
33
34
35
36
37
38
39

TORADOL® (ketorolac tromethamine)

40 RISK OF BLEEDING

- 41 ■ TORADOL inhibits platelet function and is, therefore, CONTRAINDICATED in patients
42 with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic
43 diathesis, incomplete hemostasis and those at high risk of bleeding (see **WARNINGS**
44 and **PRECAUTIONS**).

45 **46 TORADOL is contraindicated as prophylactic analgesic before any major surgery.**

48 RISK DURING LABOR AND DELIVERY

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

53 CONCOMITANT USE WITH NSAIDS

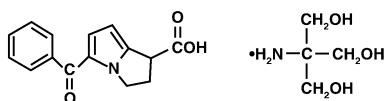
- 54 ■ TORADOL is CONTRAINDICATED in patients currently receiving aspirin or NSAIDs
55 because of the cumulative risk of inducing serious NSAID-related side effects.

56 SPECIAL POPULATIONS

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

60 DESCRIPTION

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



65 Ketonolac tromethamine is a racemic mixture of [-]S and [+]R ketonolac tromethamine.
66 Ketonolac tromethamine may exist in three crystal forms. All forms are equally soluble in
67 water. Ketonolac tromethamine has a pKa of 3.5 and an n-octanol/water partition
68 coefficient of 0.26. The molecular weight of ketonolac tromethamine is 376.41. Its
69 molecular formula is C₁₉H₂₄N₂O₆.

70 TORADOL^{ORAL} is available as round, white, film-coated, red-printed tablets. Each tablet
71 contains 10 mg ketonolac tromethamine, the active ingredient, with added lactose,
72 magnesium stearate and microcrystalline cellulose. The white film-coating contains
73 hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

TORADOL® (ketorolac tromethamine)

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 Kеторолак трометамин – это нестероидальный противовоспалительный препарат (НСАИД), который демонстрирует
84 анальгетическую активность в экспериментальных моделях животных. Механизм действия кеторолака, как и других НСАИДов, не
85 полностью понят, но может быть связан с ингибированием синтетазы простагландинов. Биологическая активность кеторолака трометамин
86 связана с S-формой. Кеторолак трометамин не обладает седативными или антистрессовыми свойствами.

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 Кеторолак трометамин – это рацемический комплекс из [-]S- и [+]R-энантиомерных форм, с S-формой
93 обладающей анальгетической активностью.

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-

TORADOL® (ketorolac tromethamine)

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 Kеторолак трометамин выделяется в грудное молоко (см. **ПРЕДУПРЕЖДЕНИЯ: Грудные**
122 **Матери).**

123 Metabolism

124 Кеторолак трометамин преимущественно метаболизируется в печени. Метаболические продукты являются
125 гидроксилированными и конъюгированными формами родительского препарата. Продукты метаболизма, а также
126 некоторые неизмененные препараты, выделяются в мочу.

127 Excretion

128 Основной путь выведения кеторолака и его метаболитов – почечный. Около 92% от дозы выделяется в мочу, при этом 40% в виде метаболитов и 60% в виде неизмененного кеторолака. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg TORADOL (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined in **Table 2** (see **CLINICAL PHARMACOLOGY: Kinetics in Special Populations**).

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 Кеторолак трометамин, введенный в виде инфузии каждые 6 часов в течение 5 дней здоровым
143 добровольцам (n=13), не показал значимой разницы в C_{max} на день 1 и день 5. Тrough
144 уровни на день 1 и день 6 были равны 0.29 µg/mL (SD ± 0.13) и 0.55 µg/mL (SD ± 0.23) соответственно. Установленный
145 состоящий состоялся после четвертой дозы.

146 Аккумуляция кеторолака трометамина не изучалась в специальных популяциях (старческая, детская, почечная или
147 печеночная недостаточность).

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) (см. **Table 2**). There was little difference in the C_{max} for the
153 two groups (elderly, 2.52 µg/mL ± 0.77; young, 2.99 µg/mL ± 1.03) (см.
154 **ПРЕДУПРЕЖДЕНИЯ: Геронтологическое применение**).

TORADOL® (ketorolac tromethamine)

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 ± 1.6 hours, the average
159 clearance was 0.042 ± 0.01 L/hr/kg, the volume of distribution during the terminal phase
160 (V_B) was 0.34 ± 0.12 L/kg and the volume of distribution at steady state (V_{ss}) was
161 0.26 ± 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_∞ 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_∞ -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_∞ 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.

TORADOL® (ketorolac tromethamine)

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 _{max} ¹ (min)	44 ± 34	33 ± 21§	44 ± 29	33 ± 21§	1.1 ± 0.7§	2.9 ± 1.8
C _{max} ² (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 _{max} (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 _{min} ³ (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 _{avg} ⁴ (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
V _B ⁵ (L/kg)	0.175 ± 0.039			0.210 ± 0.044		

% Dose metabolized = <50

% Dose excreted in feces = 6

% Dose excreted in urine = 91

% Plasma protein binding = 99

* 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_{max} and T_{max} data

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

¹Time-to-peak plasma concentration

²Peak plasma concentration

³Trough plasma concentration

⁴Average plasma concentration

⁵Volume of distribution

TORADOL® (ketorolac tromethamine)

Table 2 The Influence of Age, Liver, and Kidney Function on the Clearance and Terminal Half-life of Ketorolac Tromethamine (IM¹ and ORAL²) in Adult Populations

Type of Subjects	Total Clearance [in L/h/kg] ³		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)	—

¹ Estimated from 30 mg single IM doses of ketorolac tromethamine

² Estimated from 10 mg single oral doses of ketorolac tromethamine

³ Liters/hour/kilogram

TORADOL® (ketorolac tromethamine)

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^{IV} 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^{IV} 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^{ORAL} 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^{ORAL} 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^{ORAL} is to be used only as continuation treatment, if
213 necessary.

214 The total combined duration of use of TORADOL^{ORAL} 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^{ORAL} 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

TORADOL® (ketorolac tromethamine)

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^{ORAL} and IV or IM dosing of ketorolac
253 tromethamine is not to exceed 5 days in adults. TORADOL^{ORAL} 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

TORADOL® (ketorolac tromethamine)

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**).

TORADOL® (ketorolac tromethamine)

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

TORADOL® (ketorolac tromethamine)

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.

TORADOL® (ketorolac tromethamine)

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,

TORADOL® (ketorolac tromethamine)

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^{ORAL} to other family members and to discard any unused drug.**

426 Remember that the total combined duration of use of TORADOL^{ORAL} and IV or IM
427 dosing of ketorolac tromethamine is not to exceed 5 days in adults. TORADOL^{ORAL} 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.

TORADOL® (ketorolac tromethamine)

- 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^{ORAL} 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**).

TORADOL® (ketorolac tromethamine)

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^{ORAL} 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.

TORADOL® (ketorolac tromethamine)

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^{IV/IM} 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 Kеторолак трометамин не был мутагенным в тесте Ames, не был связан с
558 синтезом и ремонтом ДНК, и не был связан с первичными мутациями. Кеторолак трометамин не был
559 причиной разрыва хромосом в тесте микронуклеусов у мышей. При концентрации 1590 µg/mL
560 и выше, кеторолак трометамин увеличил вероятность нахождения хромосомальных аберраций в
561 яйцеклетках крыс.

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

TORADOL® (ketorolac tromethamine)

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^{ORAL} 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^{ORAL} is not indicated for use in pediatric patients. The safety and effectiveness
600 of TORADOL^{ORAL} 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

TORADOL® (ketorolac tromethamine)

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

TORADOL® (ketorolac tromethamine)

- 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, hyperkinesis, 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^{IV/IM}, demonstrated that the risk of
660 clinically serious gastrointestinal (GI) bleeding was dose-dependent (see Tables 3A and

TORADOL® (ketorolac tromethamine)

661 3B). This was particularly true in elderly patients who received an average daily dose
662 greater than 60 mg/day of ketorolac tromethamine^{IV/IM} (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^{IV/IM}**

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

Age of Patients	Total Daily Dose of Ketorolac Tromethamine ^{IV/IM}			
	≤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 ^{IV/IM}			
	≤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^{ORAL} is not to exceed 5 days. In adults, the use of TORADOL^{ORAL} is

TORADOL® (ketorolac tromethamine)

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^{ORAL}:**

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 \geq 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^{ORAL} is not to exceed 5 days.

705 The following table summarizes TORADOL^{ORAL} dosing instructions in terms of age
706 group:

707 **Table 4 Summary of Dosing Instructions**

Patient Population	TORADOL ^{ORAL} (following IV or IM dosing of ketorolac tromethamine)
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

708

709 **HOW SUPPLIED**

710 **TORADOL^{ORAL}** 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).

TORADOL® (ketorolac tromethamine)

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

(See the end of this Medication Guide
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

**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

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

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

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

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

753 Do not take an NSAID medicine:

TORADOL® (ketorolac tromethamine)

- 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)?**

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

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

TORADOL® (ketorolac tromethamine)

- 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:**

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

TORADOL® (ketorolac tromethamine)

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

809 Celebrex is a registered trademark of G.D. Searle LLC.

810 Cataflam, Voltaren are registered trademarks of Novartis Corporation.

811 Arthrotec (combined with misoprostol) is a registered trademark of G.D. Searle LLC.

812 Dolobid is a registered trademark of Merck & Co. Inc.

813 Lodine, Lodine XL are registered trademarks of Wyeth.

814 Nalfon, Nalfon 200 are registered trademarks of Pedinol Pharmacal Inc.

815 Ansaid is a registered trademark of Pharmacia & Upjohn Company LLC.

816 Motrin is a registered trademark of Johnson & Johnson.

817 Tab-Profen is a registered trademark of L. Perrigo Company.

818 Vicoprofen (combined with hydrocodone) is a registered trademark of BASF K & F
819 Corporation.

820 Combunox (combined with oxycodone) is a registered trademark of Forest Laboratories,
821 Inc.

822 Indocin, Indocin SR are registered trademarks of Merck & Co. Inc.

823 Oruvail is a registered trademark of Imperial Bank, As Agent (formerly registered to
824 Aventis Pharma S.A.).

825 Toradol is a registered trademark of Hoffmann-La Roche Inc.

826 Ponstel is a registered trademark of Lasalle National Bank Association.

827 Mobic is a registered trademark of Boehringer Ingelheim Pharma GMBG & Co. Kg.

828 Relafen is a registered trademark of SmithKline Beecham Corporation.

TORADOL® (ketorolac tromethamine)

829 Naprosyn, EC-Naprosyn, Anaprox, Anaprox DS are registered trademarks of Syntex
830 Pharmaceuticals International Ltd.

831 Naprelan is a registered trademark of Elan Corporation PLC.

832 Naprapac (copackaged with lansoprazole) is a registered trademark of Syntex
833 Pharmaceuticals International Ltd.

834 Daypro is a registered trademark of G.D. Searle LLC.

835 Feldene is a registered trademark of Pfizer.

836 Clinoril is a registered trademark of Merck & Co. Inc.

837 Tolectin, Tolectin DS, Tolectin 600 are registered trademarks of Johnson & Johnson
838 Corporation.

839

840 Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

841

842

843 xxxxxx

844 Revised: Month Year

845 Copyright © 1997-xxxx by Roche Laboratories Inc. All rights reserved.