

32 analgesia and 200 times more potent in μ -opioid binding. Tramadol-
33 induced analgesia is only partially antagonized by the opiate antagonist
34 naloxone in several animal tests. The relative contribution of both
35 tramadol and M1 to human analgesia is dependent upon the plasma
36 concentrations of each compound (see CLINICAL PHARMACOLOGY,
37 Pharmacokinetics).

38 Tramadol has been shown to inhibit reuptake of norepinephrine and
39 serotonin *in vitro*, as have some other opioid analgesics. These
40 mechanisms may contribute independently to the overall analgesic
41 profile of ULTRAM. Analgesia in humans begins approximately within
42 one hour after administration and reaches a peak in approximately two
43 to three hours.

44 Apart from analgesia, ULTRAM administration may produce a
45 constellation of symptoms (including dizziness, somnolence, nausea,
46 constipation, sweating and pruritus) similar to that of an opioid.
47 However, tramadol causes less respiratory depression than morphine
48 at recommended doses (see OVERDOSAGE). In contrast to
49 morphine, tramadol has not been shown to cause histamine release. At
50 therapeutic doses, ULTRAM has no effect on heart rate, left-ventricular
51 function or cardiac index. Orthostatic hypotension has been observed.

52 **Pharmacokinetics**

53 The analgesic activity of ULTRAM is due to both parent drug and the M1
54 metabolite (see CLINICAL PHARMACOLOGY, Pharmacodynamics).
55 Tramadol is administered as a racemate and both the [-] and [+] forms
56 of both tramadol and M1 are detected in the circulation. Tramadol is
57 well absorbed orally with an absolute bioavailability of 75%. Tramadol
58 has a volume of distribution of approximately 2.7L/kg and is only 20%
59 bound to plasma proteins. Tramadol is extensively metabolized by a
60 number of pathways, including CYP2D6 and CYP3A4, as well as by
61 conjugation of parent and metabolites. One metabolite, M1, is
62 pharmacologically active in animal models. The formation of M1 is

Tramadol HCL Tablets 50 Mg Scored
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63 dependent upon Cytochrome P-450(2D6) and as such is subject to
64 both metabolic induction and inhibition which may affect the therapeutic
65 response (see PRECAUTIONS - Drug Interactions). Tramadol and its
66 metabolites are excreted primarily in the urine with observed plasma
67 half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear
68 pharmacokinetics have been observed following multiple doses of 50
69 and 100 mg to steady-state.

70 *Absorption:*

71 Racemic tramadol is rapidly and almost completely absorbed after oral
72 administration. The mean absolute bioavailability of a 100 mg oral dose
73 is approximately 75%. The mean peak plasma concentration of
74 racemic tramadol and M1 occurs at two and three hours, respectively,
75 after administration in healthy adults. In general, both enantiomers of
76 tramadol and M1 follow a parallel time course in the body following
77 single and multiple doses although small differences (~ 10%) exist in the
78 absolute amount of each enantiomer present.

79 Steady-state plasma concentrations of both tramadol and M1 are
80 achieved within two days with q.i.d. dosing. There is no evidence of
81 self-induction (see Figure 1 and Table 1 below).

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[Figure 1]

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Table 1
Mean (%CV) Pharmacokinetic Parameters for
Racemic Tramadol and M1 Metabolite

Population/ Dosage Regimen ^a	Parent Drug/ Metabolite	Peak Conc. (ng/mL)	Time to Peak (hrs)	Clearance/F ^b (mL/min/Kg)	t _{1/2} (hrs)
Healthy Adults, 100 mg qid, MD p.o.	Tramadol	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
	M1	110 (29)	2.4 (46)	c	7.0 (14)
Healthy Adults, 100 mg SD p.o.	Tramadol	308 (25)	1.6 (63)	8.50 (31)	5.6 (20)
	M1	55.0 (36)	3.0 (51)	c	6.7 (16)
Geriatric, (>75 yrs) 50 mg SD p.o.	Tramadol	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
	M1	d	d	c	d
Hepatic Impaired, 50 mg SD p.o.	Tramadol	217 (11)	1.9 (16)	4.23 (56)	13.3 (11)
	M1	19.4 (12)	9.8 (20)	c	18.5 (15)
Renal Impaired, CL _{cr} 10-30 mL/min 100 mg SD i.v.	Tramadol	c	c	4.23 (54)	10.6 (31)
	M1	c	c	c	11.5 (40)
Renal Impaired, CL _{cr} <5 mL/min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)	11.0 (29)
	M1	c	c	c	16.9 (18)

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- a SD = Single dose, MD = Multiple dose, p.o.= Oral administration,
i.v.= Intravenous administration, q.i.d. = Four times daily
- b F represents the oral bioavailability of tramadol
- c Not applicable
- d Not measured

95 *Food Effects:* Oral administration of ULTRAM with food does not
96 significantly affect its rate or extent of absorption, therefore, ULTRAM
97 can be administered without regard to food.

98 *Distribution:*

99 The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male
100 and female subjects, respectively, following a 100 mg intravenous dose.
101 The binding of tramadol to human plasma proteins is approximately
102 20% and binding also appears to be independent of concentration up to
103 10 µg/mL. Saturation of plasma protein binding occurs only at
104 concentrations outside the clinically relevant range. Although not
105 confirmed in humans, tramadol has been shown in rats to cross the
106 blood-brain barrier.

107 *Metabolism:*

108 Tramadol is extensively metabolized after oral administration.
109 Approximately 30% of the dose is excreted in the urine as unchanged
110 drug, whereas 60% of the dose is excreted as metabolites. The
111 remainder is excreted either as unidentified or as unextractable
112 metabolites. The major metabolic pathways appear to be *N*- and *O*-
113 demethylation and glucuronidation or sulfation in the liver. One
114 metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically
115 active in animal models. Production of M1 is dependent on the CYP2D6
116 isoenzyme of cytochrome P450 and as such is subject to both
117 metabolic induction and inhibition which may affect the therapeutic
118 response (see PRECAUTIONS - Drug Interaction).

119 Approximately 7% of the population has reduced activity of the CYP2D6
120 isoenzyme of cytochrome P-450. These individuals are "poor
121 metabolizers" of debrisoquine, dextromethorphan, tricyclic
122 antidepressants, among other drugs. After a single oral dose of
123 tramadol, concentrations of tramadol were only slightly higher in "poor
124 metabolizers" versus "extensive metabolizers", while M1 concentrations
125 were lower. Concomitant therapy with inhibitors of CYP2D6 such as

126 fluoxetine, paroxetine and quinidine could result in significant drug
127 interactions. In vitro drug interaction studies in human liver microsomes
128 indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite
129 norfluoxetine, amitriptyline and quinidine inhibit the metabolism of
130 tramadol to various degrees, suggesting that concomitant
131 administration of these compounds could result in increases in tramadol
132 concentrations and decreased concentrations of M1. The
133 pharmacological impact of these alterations in terms of either efficacy
134 or safety is unknown.

135 *Elimination:*

136 The mean terminal plasma elimination half-lives of racemic tramadol
137 and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The
138 plasma elimination half-life of racemic tramadol increased from
139 approximately six hours to seven hours upon multiple dosing.

140 **Special Populations**

141 *Renal:*

142 Impaired renal function results in a decreased rate and extent of
143 excretion of tramadol and its active metabolite, M1. In patients with
144 creatinine clearances of less than 30 mL/min, adjustment of the dosing
145 regimen is recommended (see DOSAGE AND ADMINISTRATION).
146 The total amount of tramadol and M1 removed during a 4-hour dialysis
147 period is less than 7% of the administered dose.

148 *Hepatic:*

149 Metabolism of tramadol and M1 is reduced in patients with advanced
150 cirrhosis of the liver, resulting in both a larger area under the
151 concentration time curve for tramadol and longer tramadol and M1
152 elimination half-lives (13 hr. for tramadol and 19 hr. for M1). In cirrhotic
153 patients, adjustment of the dosing regimen is recommended (see
154 DOSAGE AND ADMINISTRATION).

155 *Age:*

156 Healthy elderly subjects aged 65 to 75 years have plasma tramadol
157 concentrations and elimination half-lives comparable to those observed
158 in healthy subjects less than 65 years of age. In subjects over 75 years,
159 maximum serum concentrations are slightly elevated (208 vs. 162
160 ng/mL) and the elimination half-life is slightly prolonged (7 vs. 6 hours)
161 compared to subjects 65 to 75 years of age. Adjustment of the daily
162 dose is recommended for patients older than 75 years (see DOSAGE
163 AND ADMINISTRATION).

164 *Gender:*

165 The absolute bioavailability of tramadol was 73% in males and 79% in
166 females. The plasma clearance was 6.4 mL/min/kg in males and 5.7
167 mL/min/kg in females following a 100 mg IV dose of tramadol.
168 Following a single oral dose, and after adjusting for body weight,
169 females had a 12% higher peak tramadol concentration and a 35%
170 higher area under the concentration-time curve compared to males.
171 The clinical significance of this difference is unknown.

172 **Clinical Studies**

173 ULTRAM has been given in single oral doses of 50, 75, 100, 150 and
174 200 mg to patients with pain following surgical procedures and pain
175 following oral surgery (extraction of impacted molars).

176 In single-dose models of pain following oral surgery, pain relief was
177 demonstrated in some patients at doses of 50 mg and 75 mg. A dose
178 of 100 mg ULTRAM tended to provide analgesia superior to codeine
179 sulfate 60 mg, but it was not as effective as the combination of aspirin
180 650 mg with codeine phosphate 60 mg. In single-dose models of pain
181 following surgical procedures, 150 mg provided analgesia generally
182 comparable to the combination of acetaminophen 650 mg with
183 propoxyphene napsylate 100 mg, with a tendency toward later peak
184 effect.

185 ULTRAM has been studied in three long-term controlled trials
186 involving a total of 820 patients, with 530 patients receiving ULTRAM.

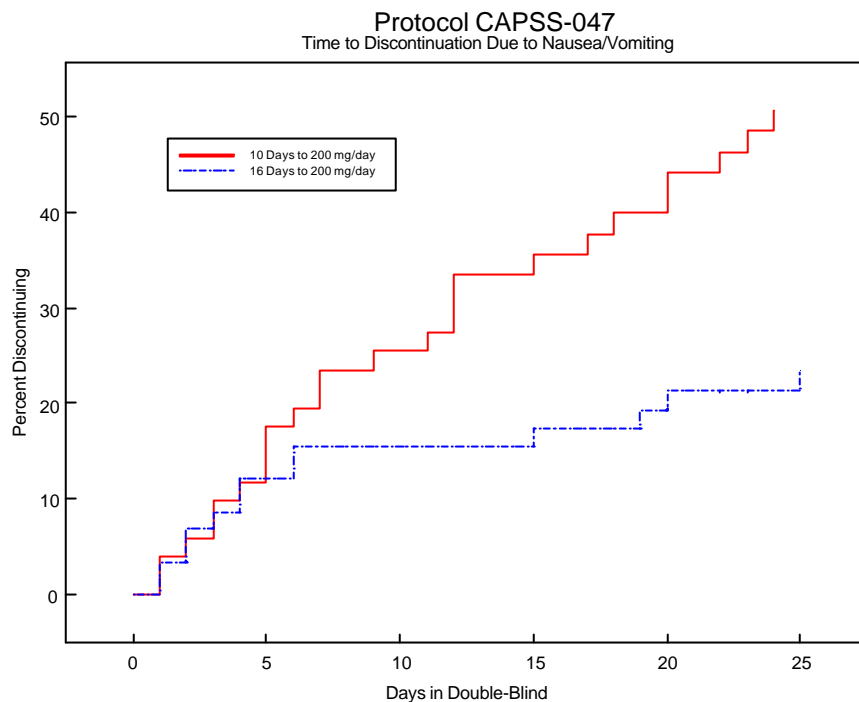
187 Patients with a variety of chronic painful conditions were studied in
188 double-blind trials of one to three months duration. Average daily doses
189 of approximately 250 mg of ULTRAM in divided doses were generally
190 comparable to five doses of acetaminophen 300 mg with codeine
191 phosphate 30 mg (TYLENOL[®] with Codeine #3) daily, five doses of
192 aspirin 325 mg with codeine phosphate 30 mg daily, or two to three
193 doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg
194 (TYLOX[®]) daily.

195 **Titration Trials**

196 In a randomized, blinded clinical study with 129 to 132 patients per
197 group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg
198 q.i.d.), attained in 50 mg increments every 3 days, was found to result in
199 fewer discontinuations due to dizziness or vertigo than titration over only
200 4 days or no titration. In a second study with 54 to 59 patients per
201 group, patients who had nausea or vomiting when titrated over 4 days
202 were randomized to re-initiate ULTRAM therapy using slower titration
203 rates. A 16-day titration schedule, starting with 25 mg qAM and using
204 additional doses in 25 mg increments every third day to 100 mg/day (25
205 mg q.i.d.), followed by 50 mg increments in the total daily dose every
206 third day to 200 mg/day (50 mg q.i.d.), resulted in fewer
207 discontinuations due to nausea or vomiting and fewer discontinuations
208 due to any cause than did a 10-day titration schedule.

209

Figure 2



210

INDICATIONS AND USAGE

211

212 ULTRAM is indicated for the management of moderate to moderately
213 severe pain.

214

CONTRAINDICATIONS

215

216 ULTRAM should not be administered to patients who have previously
217 demonstrated hypersensitivity to tramadol, any other component of this
218 product or opioids. It is also contraindicated in cases of acute
219 intoxication with alcohol, hypnotics, centrally acting analgesics, opioids
220 or psychotropic drugs.

221

222 **WARNINGS**

223 **Seizure Risk**

224 **Seizures have been reported in patients receiving ULTRAM**
225 **within the recommended dosage range. Spontaneous post-**
226 **marketing reports indicate that seizure risk is increased with**
227 **doses of ULTRAM above the recommended range. Concomitant**
228 **use of ULTRAM increases the seizure risk in patients taking:**

- 229 • **Selective serotonin reuptake inhibitors (SSRI**
230 **antidepressants or anorectics),**
- 231 • **Tricyclic antidepressants (TCAs), and other tricyclic**
232 **compounds (e.g., cyclobenzaprine, promethazine, etc.),**
233 **or**
- 234 • **Opioids.**

235 **Administration of ULTRAM may enhance the seizure risk in**
236 **patients taking:**

- 237 • **MAO inhibitors (see also WARNINGS - Use with MAO**
238 **Inhibitors),**
- 239 • **Neuroleptics, or**
- 240 • **Other drugs that reduce the seizure threshold.**

241 **Risk of convulsions may also increase in patients with epilepsy,**
242 **those with a history of seizures, or in patients with a recognized**
243 **risk for seizure (such as head trauma, metabolic disorders,**
244 **alcohol and drug withdrawal, CNS infections). In ULTRAM**
245 **overdose, naloxone administration may increase the risk of**
246 **seizure.**

247 **Anaphylactoid Reactions**

248 **Serious and rarely fatal anaphylactoid reactions have been reported in**
249 **patients receiving therapy with ULTRAM. These reactions often occur**
250 **following the first dose. Other reported reactions include pruritus, hives,**
251 **bronchospasm, and angioedema. Patients with a history of**
252 **anaphylactoid reactions to codeine and other opioids may be at**

253 increased risk and therefore should not receive ULTRAM (see
254 CONTRAINDICATIONS).

255 **Use in Opioid-dependent Patients**

256 ULTRAM should not be used in opioid-dependent patients. ULTRAM
257 has been shown to reinitiate physical dependence in some patients that
258 have been previously dependent on other opioids. Consequently, in
259 patients with a tendency to opioid abuse or opioid dependence,
260 treatment with ULTRAM is not recommended.

261 **Use with CNS Depressants**

262 ULTRAM should be used with caution and in reduced dosages when
263 administered to patients receiving CNS depressants such as alcohol,
264 opioids, anesthetic agents, phenothiazines, tranquilizers or sedative
265 hypnotics.

266 **Use with MAO Inhibitors**

267 Use ULTRAM with great caution in patients taking monoamine oxidase
268 inhibitors, because animal studies have shown increased deaths with
269 combined administration.

270

271 **PRECAUTIONS**

272 **Respiratory Depression**

273 Administer ULTRAM cautiously in patients at risk for respiratory
274 depression. When large doses of ULTRAM are administered with
275 anesthetic medications or alcohol, respiratory depression may result.

276 Treat such cases as an overdose. If naloxone is to be administered,
277 use cautiously because it may precipitate seizures (see WARNINGS,
278 Seizure Risk and OVERDOSAGE).

279 **Increased Intracranial Pressure or Head Trauma**

280 ULTRAM should be used with caution in patients with increased
281 intracranial pressure or head injury. Pupillary changes (miosis) from
282 tramadol may obscure the existence, extent, or course of intracranial
283 pathology. Clinicians should also maintain a high index of suspicion for

284 adverse drug reaction when evaluating altered mental status in these
285 patients if they are receiving ULTRAM.

286 **Acute Abdominal Conditions**

287 The administration of ULTRAM may complicate the clinical assessment
288 of patients with acute abdominal conditions.

289 **Withdrawal**

290 Withdrawal symptoms may occur if ULTRAM is discontinued abruptly.
291 These symptoms may include: anxiety, sweating, insomnia, rigors, pain,
292 nausea, tremors, diarrhoea, upper respiratory symptoms, piloerection,
293 and rarely hallucinations. Clinical experience suggests that withdrawal
294 symptoms may be relieved by tapering the medication.

295 **Patients Physically Dependent on Opioids**

296 ULTRAM is not recommended for patients who are dependent on
297 opioids. Patients who have recently taken substantial amounts of
298 opioids may experience withdrawal symptoms. Because of the difficulty
299 in assessing dependence in patients who have previously received
300 substantial amounts of opioid medication, administer ULTRAM
301 cautiously to such patients.

302 **Use in Renal and Hepatic Disease**

303 Impaired renal function results in a decreased rate and extent of
304 excretion of tramadol and its active metabolite, M1. In patients with
305 creatinine clearances of less than 30 mL/min, dosing reduction is
306 recommended (see DOSAGE AND ADMINISTRATION).

307 Metabolism of tramadol and M1 is reduced in patients with advanced
308 cirrhosis of the liver. In cirrhotic patients, dosing reduction is
309 recommended (see DOSAGE AND ADMINISTRATION).

310 With the prolonged half-life in these conditions, achievement of steady-
311 state is delayed, so that it may take several days for elevated plasma
312 concentrations to develop.

313 **Information for Patients**

- 314 • ULTRAM (tramadol hydrochloride tablets) may impair mental or
315 physical abilities required for the performance of potentially
316 hazardous tasks such as driving a car or operating machinery.
317 • ULTRAM should not be taken with alcohol containing beverages.
318 • ULTRAM should be used with caution when taking medications such
319 as tranquilizers, hypnotics or other opiate containing analgesics.
320 • The patient should be instructed to inform the physician if they are
321 pregnant, think they might become pregnant, or are trying to become
322 pregnant (see PRECAUTIONS: Labor and Delivery).
323 • The patient should understand the single-dose and 24-hour dose
324 limit and the time interval between doses, since exceeding these
325 recommendations can result in respiratory depression and seizures.
326

327 **Drug Interactions**

328 Tramadol does not appear to induce its own metabolism in humans,
329 since observed maximal plasma concentrations after multiple oral
330 doses are higher than expected based on single-dose data. Tramadol
331 is a mild inducer of selected drug metabolism pathways measured in
332 animals.

333 *Use with Carbamazepine*

334 Concomitant administration of ULTRAM with **carbamazepine**
335 causes a significant increase in tramadol metabolism, presumably
336 through metabolic induction by carbamazepine. Patients receiving
337 chronic carbamazepine doses of up to 800 mg daily may require up to
338 twice the recommended dose of ULTRAM.

339 *Use with Quinidine*

340 Tramadol is metabolized to M1 by the CYP2D6 P-450 isoenzyme.
341 **Quinidine** is a selective inhibitor of that isoenzyme, so that concomitant
342 administration of quinidine and ULTRAM results in increased
343 concentrations of tramadol and reduced concentrations of M1. The
344 clinical consequences of these findings are unknown. In vitro drug

345 interaction studies in human liver microsomes indicate that tramadol
346 has no effect on quinidine metabolism.

347 *Use with Inhibitors of CYP2D6*

348 In vitro drug interaction studies in human liver microsomes indicate
349 that concomitant administration with inhibitors of CYP2D6 such as
350 fluoxetine, paroxetine, and amitriptyline could result in some inhibition of
351 the metabolism of tramadol.

352 *Use with Cimetidine*

353 Concomitant administration of ULTRAM with **cimetidine** does not
354 result in clinically significant changes in tramadol pharmacokinetics.
355 Therefore, no alteration of the ULTRAM dosage regimen is
356 recommended.

357 *Use with MAO Inhibitors*

358 Interactions with **MAO Inhibitors**, due to interference with
359 detoxification mechanisms, have been reported for some centrally
360 acting drugs (see WARNINGS, Use with MAO Inhibitors).

361 *Use with Digoxin and Warfarin*

362 Post-marketing surveillance has revealed rare reports of digoxin
363 toxicity and alteration of warfarin effect, including elevation of
364 prothrombin times.

365 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

366 Tramadol was not mutagenic in the following assays: Ames *Salmonella*
367 microsomal activation test, CHO/HPRT mammalian cell assay, mouse
368 lymphoma assay (in the absence of metabolic activation), dominant
369 lethal mutation tests in mice, chromosome aberration test in Chinese
370 hamsters, and bone marrow micronucleus tests in mice and Chinese
371 hamsters. Weakly mutagenic results occurred in the presence of
372 metabolic activation in the mouse lymphoma assay and micronucleus
373 test in rats. Overall, the weight of evidence from these tests indicates
374 that tramadol does not pose a genotoxic risk to humans.

375 A slight, but statistically significant, increase in two common murine
376 tumors, pulmonary and hepatic, was observed in a mouse
377 carcinogenicity study, particularly in aged mice (dosing orally up to 30
378 mg/kg for approximately two years, although the study was not done with
379 the Maximum Tolerated Dose). This finding is not believed to suggest
380 risk in humans. No such finding occurred in a rat carcinogenicity study.

381 No effects on fertility were observed for tramadol at oral dose levels
382 up to 50 mg/kg in male rats and 75 mg/kg in female rats.

383

384 **Pregnancy, Teratogenic Effects:** *Pregnancy Category C*

385 There are no adequate and well-controlled studies in pregnant women.
386 ULTRAM should be used during pregnancy only if the potential benefit
387 justifies the potential risk to the fetus.

388 Tramadol has been shown to be embryotoxic and fetotoxic in mice,
389 rats and rabbits at maternally toxic doses 3 to 15 times the maximum
390 human dose or higher (120 mg/kg in mice, 25 mg/kg or higher in rats
391 and 75 mg/kg or higher in rabbits), but was not teratogenic at these
392 dose levels. No harm to the fetus due to tramadol was seen at doses
393 that were not maternally toxic.

394 No drug-related teratogenic effects were observed in progeny of
395 mice, rats or rabbits treated with tramadol by various routes (up to 140

396 mg/kg for mice, 80 mg/kg for rats or 300 mg/kg for rabbits). Embryo
397 and fetal toxicity consisted primarily of decreased fetal weights, skeletal
398 ossification and increased supernumerary ribs at maternally toxic dose
399 levels. Transient delays in developmental or behavioral parameters
400 were also seen in pups from rat dams allowed to deliver. Embryo and
401 fetal lethality were reported only in one rabbit study at 300 mg/kg, a
402 dose that would cause extreme maternal toxicity in the rabbit.

403 In peri- and post-natal studies in rats, progeny of dams receiving oral
404 (gavage) dose levels of 50 mg/kg or greater had decreased weights,
405 and pup survival was decreased early in lactation at 80 mg/kg (6 to 10
406 times the maximum human dose). No toxicity was observed for progeny
407 of dams receiving 8, 10, 20, 25 or 40 mg/kg. Maternal toxicity was
408 observed at all dose levels, but effects on progeny were evident only at
409 higher dose levels where maternal toxicity was more severe.

410 **Labor and Delivery**

411 ULTRAM should not be used in pregnant women prior to or during labor
412 unless the potential benefits outweigh the risks. Safe use in pregnancy
413 has not been established. Chronic use during pregnancy may lead to
414 physical dependence and post-partum withdrawal symptoms in the
415 newborn. Tramadol has been shown to cross the placenta. The mean
416 ratio of serum tramadol in the umbilical veins compared to maternal
417 veins was 0.83 for 40 women given tramadol during labor.

418 The effect of ULTRAM, if any, on the later growth, development, and
419 functional maturation of the child is unknown.

420 **Nursing Mothers**

421 ULTRAM is not recommended for obstetrical preoperative medication
422 or for post-delivery analgesia in nursing mothers because its safety in
423 infants and newborns has not been studied. Following a single IV 100
424 mg dose of tramadol, the cumulative excretion in breast milk within 16
425 hours postdose was 100 µg of tramadol (0.1% of the maternal dose)
426 and 27 µg of M1.

427 **Pediatric Use**

428 The pediatric use of ULTRAM is not recommended because safety and
429 efficacy in patients under 16 years of age have not been established.

430 **Use in the Elderly**

431 In subjects over the age of 75 years, serum concentrations are slightly
432 elevated and the elimination half-life is slightly prolonged. The aged
433 also can be expected to vary more widely in their ability to tolerate
434 adverse drug effects. Daily doses in excess of 300 mg are not
435 recommended in patients over 75 (see DOSAGE AND
436 ADMINISTRATION).

437

438 **ADVERSE REACTIONS**

439 ULTRAM was administered to 550 patients during the double-blind or
440 open-label extension periods in U.S. studies of chronic nonmalignant
441 pain. Of these patients, 375 were 65 years old or older. Table 2
442 reports the cumulative incidence rate of adverse reactions by 7, 30 and
443 90 days for the most frequent reactions (5% or more by 7 days). The
444 most frequently reported events were in the central nervous system and
445 gastrointestinal system. Although the reactions listed in the table are felt
446 to be probably related to ULTRAM administration, the reported rates
447 also include some events that may have been due to underlying disease
448 or concomitant medication. The overall incidence rates of adverse
449 experiences in these trials were similar for ULTRAM and the active
450 control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg

451 with codeine phosphate 30 mg), and aspirin 325 mg with codeine
452 phosphate 30 mg.

453

454

455

456

Table 2
Cumulative Incidence of Adverse Reactions for ULTRAM in
Chronic Trials of Nonmalignant Pain. (N=427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation" ¹	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

457

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466

¹ "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Incidence 1% to less than 5%, possibly causally related: the following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists.

Body as a Whole: Malaise.

Cardiovascular: Vasodilation.

467 **Central Nervous System:** Anxiety, Confusion, Coordination
468 disturbance, Euphoria, Nervousness, Sleep disorder.

469 **Gastrointestinal:** Abdominal pain, Anorexia, Flatulence.

470 **Musculoskeletal:** Hypertonia.

471 **Skin:** Rash.

472 **Special Senses:** Visual disturbance.

473 **Urogenital:** Menopausal symptoms, Urinary frequency, Urinary
474 retention.

475

476 *Incidence less than 1%, possibly causally related:* the following lists
477 adverse reactions that occurred with an incidence of less than 1% in
478 clinical trials and/or reported in post-marketing experience.

479 **Body as a Whole:** Accidental injury, Allergic reaction, Anaphylaxis,
480 Suicidal tendency, Weight loss.

481 **Cardiovascular:** Orthostatic hypotension, Syncope, Tachycardia.

482 **Central Nervous System:** Abnormal gait, Amnesia, Cognitive
483 dysfunction, Depression, Difficulty in concentration, Hallucinations,
484 Paresthesia, Seizure (see WARNINGS), Tremor.

485 **Respiratory:** Dyspnea.

486 **Skin:** Stevens-Johnson syndrome/Toxic epidermal necrolysis,
487 Urticaria, Vesicles.

488 **Special Senses:** Dysgeusia.

489 **Urogenital:** Dysuria, Menstrual disorder.

490

491 *Other adverse experiences, causal relationship unknown:* A variety of
492 other adverse events were reported infrequently in patients taking
493 ULTRAM during clinical trials and/or reported in post-marketing
494 experience. A causal relationship between ULTRAM and these events
495 has not been determined. However, the most significant events are
496 listed below as alerting information to the physician.

497 **Cardiovascular:** Abnormal ECG, Hypertension, Hypotension,

498 Myocardial ischemia, Palpitations.

499 **Central Nervous System:** Migraine, Speech disorders.

500 **Gastrointestinal:** Gastrointestinal bleeding, Hepatitis, Stomatitis.

501 **Laboratory Abnormalities:** Creatinine increase, Elevated liver
502 enzymes, Hemoglobin decrease, Proteinuria.

503 **Sensory:** Cataracts, Deafness, Tinnitus.

504

505 **DRUG ABUSE AND DEPENDENCE**

506 ULTRAM has a potential to cause psychic and physical dependence of
507 the morphine-type (μ -opioid). The drug has been associated with
508 craving, drug-seeking behavior and tolerance development. Cases of
509 abuse and dependence on ULTRAM have been reported. ULTRAM
510 should not be used in opioid-dependent patients. ULTRAM can
511 reinstitute physical dependence in patients that have been previously
512 dependent or chronically using other opioids. In patients with a
513 tendency to drug abuse, a history of drug dependence, or are
514 chronically using opioids, treatment with ULTRAM is not recommended.

515

516 **OVERDOSAGE**

517 Cases of overdose with tramadol have been reported. Estimates of
518 ingested dose in foreign fatalities have been in the range of 3 to 5 g. A
519 3 g intentional overdose by a patient in the clinical studies produced
520 emesis and no sequelae. The lowest dose reported to be associated
521 with fatality was possibly between 500 and 1000 mg in a 40 kg woman,
522 but details of the case are not completely known.

523 Serious potential consequences of overdosage are respiratory
524 depression and seizure. In treating an overdose, primary attention
525 should be given to maintaining adequate ventilation along with general
526 supportive treatment. While naloxone will reverse some, but not all,
527 symptoms caused by overdosage with ULTRAM the risk of seizures is
528 also increased with naloxone administration. In animals convulsions

529 following the administration of toxic doses of tramadol could be
530 suppressed with barbiturates or benzodiazepines but were increased
531 with naloxone. Naloxone administration did not change the lethality of
532 an overdose in mice. Hemodialysis is not expected to be helpful in an
533 overdose because it removes less than 7% of the administered dose in
534 a 4-hour dialysis period.

535

536 **DOSAGE AND ADMINISTRATION**

537 For patients with moderate to moderately severe chronic pain not
538 requiring rapid onset of analgesic effect, the tolerability of ULTRAM can
539 be improved by initiating therapy with the following titration regimen:
540 ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg
541 increments as separate doses every 3 days to reach 100 mg/day (25
542 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg
543 as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After
544 titration, ULTRAM 50 to 100 mg can be administered as needed for
545 pain relief every 4 to 6 hours **not to exceed 400 mg/day**.

546

547 For the subset of patients for whom rapid onset of analgesic effect is
548 required and for whom the benefits outweigh the risk of discontinuation
549 due to adverse events associated with higher initial doses, ULTRAM 50
550 mg to 100 mg can be administered as needed for pain relief every four
551 to six hours, **not to exceed 400 mg per day**.

552

553 **Individualization of Dose**

554 Available data do not suggest that a dosage adjustment is necessary in
555 elderly patients 65 to 75 years of age unless they also have renal or
556 hepatic impairment. For elderly patients **over 75 years old**, not more
557 than 300 mg/day in divided doses as above is recommended. In all
558 patients with **creatinine clearance less than 30 mL/min**, it is
559 recommended that the dosing interval of ULTRAM be increased to 12

Tramadol HCL Tablets 50 Mg Scored
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560 hours, with a maximum daily dose of 200 mg. Since only 7% of an
561 administered dose is removed by hemodialysis, **dialysis patients** can
562 receive their regular dose on the day of dialysis. The recommended
563 dose for patients with **cirrhosis** is 50 mg every 12 hours. Patients
564 receiving chronic **carbamazepine** doses up to 800 mg daily may
565 require up to twice the recommended dose of ULTRAM.

566
567

HOW SUPPLIED

568 ULTRAM (tramadol hydrochloride tablets) Tablets - 50 mg (white,
569 scored, film-coated capsule-shaped tablet) debossed "ULTRAM" on
570 one side and "06 59" on the other side.

571
572 100's NDC 0045-0659-60 bottles of 100 tablets

573 500's NDC 0045-0659-70 bottles of 500 tablets

574 packages of 100 unit doses in blister packs - NDC 0045-0659-10 (10
575 cards of 10 tablets each).

576

577 Dispense in a tight container. Store at controlled room temperature (up
578 to 25°C, 77°F).

579

580

581 **<space allocated for Ortho-McNeil logo>**

582

583

584 **ORTHO-McNEIL**

585 **PHARMACEUTICAL, INC.**

586 **Raritan, New Jersey 08869**

587

588 U.S. Patents 3,652,589 and 3,830,934

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