

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-693**

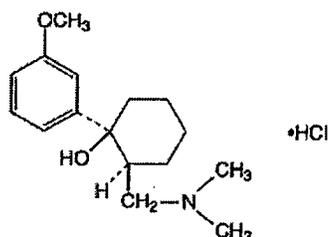
**LABELING**

1

2 **TRADE NAME**

3 **DESCRIPTION**

4 **TRADE NAME** tramadol hydrochloride orally disintegrating tablets is a centrally acting  
5 analgesic in an orally disintegrating formulation using a tablet formulation base. The  
6 chemical name for tramadol hydrochloride is ( $\pm$ ) *cis* -2-[(dimethylamino)methyl]-1-(3-  
7 methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



9 **TRADE NAME** is supplied as orally disintegrating tablets containing 50 mg of tramadol  
10 hydrochloride for oral administration.

11 Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily  
12 soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition  
13 coefficient (logP) is 1.35 at pH 7.

14 The tablets are white in color and contain the inactive ingredients aspartame, copovidone,  
15 crospovidone, ethylcellulose, magnesium stearate, mannitol, mint flavor, and silicon  
16 dioxide.

17 **CLINICAL PHARMACOLOGY**

18 **Pharmacodynamics**

19 **TRADE NAME** is a centrally acting synthetic opioid analgesic in an orally disintegrating  
20 tablet form. Although its mode of action is not completely understood, from animal tests,  
21 at least two complementary mechanisms appear applicable: binding of parent and M1  
22 metabolite to  $\mu$ -opioid receptors and weak inhibition of reuptake of norepinephrine and  
23 serotonin.

24 Opioid activity is due to both low affinity binding of the parent compound and higher  
25 affinity binding of the O-demethylated metabolite M1 to  $\mu$ -opioid receptors. In animal  
26 models, M1 is up to 6 times more potent than tramadol in producing analgesia and

27 200 times more potent in  $\mu$ -opioid binding. Tramadol-induced analgesia is only partially  
28 antagonized by the opiate antagonist naloxone in several animal tests. The relative  
29 contribution of both tramadol and M1 to human analgesia is dependent upon the plasma  
30 concentrations of each compound (see CLINICAL PHARMACOLOGY ,  
31 Pharmacokinetics).

32 Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as  
33 have some other opioid analgesics. These mechanisms may contribute independently to  
34 the overall analgesic profile of tramadol. Analgesia in humans begins approximately  
35 within one hour after administration and reaches a peak in approximately two to three  
36 hours.

37 Apart from analgesia, tramadol administration may produce a constellation of symptoms  
38 (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to  
39 that of other opioids. In contrast to morphine, tramadol has not been shown to cause  
40 histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-  
41 ventricular function or cardiac index. Orthostatic hypotension has been observed.

#### 42 **Pharmacokinetics**

43 The analgesic activity of tramadol is due to both parent drug and the M1 metabolite (see  
44 CLINICAL PHARMACOLOGY , Pharmacodynamics ). Tramadol is administered as a  
45 racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the  
46 circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%.  
47 Tramadol has a volume of distribution of approximately 2.7 L/kg and is 20% bound to  
48 plasma proteins. Tramadol is extensively metabolized by a number of pathways,  
49 including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites.  
50 One metabolite, M1, is pharmacologically active in animal models. The formation of M1  
51 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the  
52 therapeutic response (see PRECAUTIONS , Drug Interactions ). Tramadol and its  
53 metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and  
54 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been  
55 observed following multiple doses of 50 and 100 mg to steady-state.

56 No difference has been identified in systemic exposure (AUC), peak exposure ( $C_{max}$ ),  
57 time to peak exposure ( $T_{max}$ ), and apparent elimination half-life ( $t_{1/2}$ ) of tramadol and  
58 metabolites M1 and M5 between administration of TRADE NAME with and without  
59 water and Ultram®.

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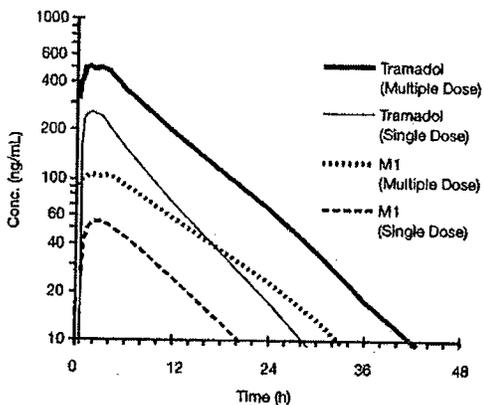
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61 *Absorption:*

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

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

72 Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg  
 73 Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given q.i.d.



74

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

Population/ Dosage Regimen <sup>a</sup>	Parent Drug/ Metabolite	Peak Conc. (ng/mL)	Time to Peak (hrs)	Clearance/F <sup>b</sup> (mL/min/Kg)	t <sub>1/2</sub> (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)	<sup>c</sup>	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)	<sup>c</sup>	6.7 (16)
Geriatric, (>75 yrs) 50 mg SD p.o.	Tramadol	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
	M1	<sup>d</sup>	<sup>d</sup>	<sup>c</sup>	<sup>d</sup>
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)	<sup>c</sup>	18.5 (15)

Renal Impaired, CL <sub>cr</sub> 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 <sub>cr</sub> <5 mL/min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)	11.0 (29)
	M1	c	c	c	16.9 (18)

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

77

78 *Food Effects:* Oral administration of TRADE NAME with food does not significantly  
79 affect its extent of absorption, however, food does delay t<sub>max</sub> by about 30 minutes  
80 compared to fasting conditions. The clinical significance of this delay is not known.

81 *Distribution:*

82 The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female  
83 subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to  
84 human plasma proteins is approximately 20% and binding also appears to be independent  
85 of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at  
86 concentrations outside the clinically relevant range.

87 *Metabolism:*

88 Tramadol is extensively metabolized after oral administration. Approximately 30% of the  
89 dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as  
90 metabolites. The remainder is excreted either as unidentified or as unextractable  
91 metabolites. The major metabolic pathways appear to be N - and O - demethylation and  
92 glucuronidation or sulfation in the liver. One metabolite ( O -desmethyltramadol, denoted  
93 M1) is pharmacologically active in animal models. Formation of M1 is dependent on  
94 CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response  
95 (see PRECAUTIONS , Drug Interaction ).

96 Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of  
97 cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine,  
98 dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population  
99 PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were  
100 approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while  
101 M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6

102 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions.  
103 In vitro drug interaction studies in human liver microsomes indicate that inhibitors of  
104 CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine  
105 inhibit the metabolism of tramadol to various degrees, suggesting that concomitant  
106 administration of these compounds could result in increases in tramadol concentrations  
107 and decreased concentrations of M1. The full pharmacological impact of these alterations  
108 in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN  
109 re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse  
110 events, including seizure (see WARNINGS ) and serotonin syndrome.

111 *Elimination:*

112 Tramadol is eliminated primarily through metabolism by the liver and the metabolites are  
113 eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of  
114 racemic tramadol and racemic M1 are  $6.3 \pm 1.4$  and  $7.4 \pm 1.4$  hours, respectively. The  
115 plasma elimination half-life of racemic tramadol increased from approximately six hours  
116 to seven hours upon multiple dosing.

117 Special Populations

118 *Renal:*

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

124 *Hepatic:*

125 Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the  
126 liver, resulting in both a larger area under the concentration time curve for tramadol and  
127 longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1).  
128 In cirrhotic patients, adjustment of the dosing regimen is recommended (see DOSAGE  
129 AND ADMINISTRATION ).

130 *Geriatric:*

131 Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and  
132 elimination half-lives comparable to those observed in healthy subjects less than 65 years  
133 of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs.  
134 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to  
135 subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients  
136 older than 75 years (see DOSAGE AND ADMINISTRATION ).

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137 *Gender:*

138 Following a single oral dose of TRADE NAME to healthy volunteers, no gender effect  
139 was observed. The AUC and  $C_{max}$  values for TRADE NAME were similar in males and  
140 females. Dosage adjustment based on gender is not recommended.

141 The absolute bioavailability of tramadol was 73% in males and 79% in females. The  
142 plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a  
143 100 mg intravenous dose of tramadol.

144 **CLINICAL STUDIES**

145 TRADE NAME is an orally disintegrating tablet, but there are no studies that indicate  
146 that its onset of action is faster than tramadol tablets.

147 An orally swallowed immediate release tablet of tramadol has been given in single oral  
148 doses of 50, 75 and 100 mg to patients with pain following surgical procedures and pain  
149 following oral surgery (extraction of impacted molars). In single-dose models of pain  
150 following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg  
151 and 75 mg. A dose of 100 mg of orally swallowed immediate release tablet of tramadol  
152 tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective  
153 as the combination of aspirin 650 mg with codeine phosphate 60 mg.

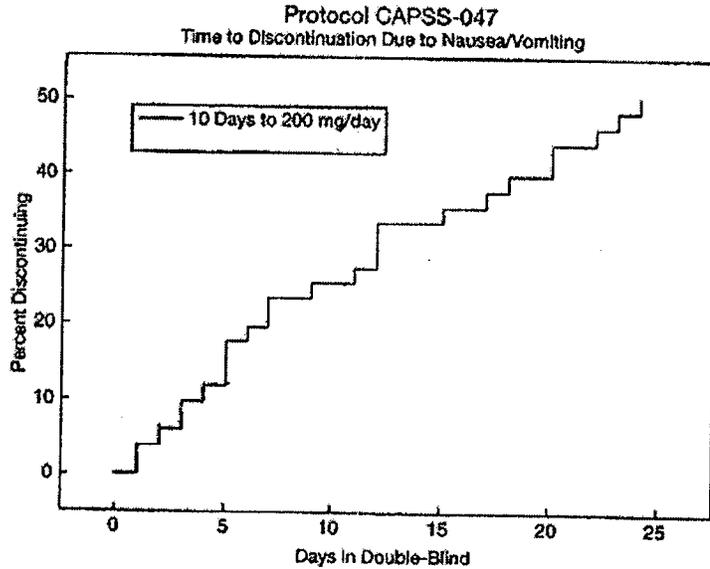
154  
155 An orally swallowed immediate release tablet of tramadol has been studied in three long-  
156 term controlled trials involving a total of 820 patients, with 530 patients receiving an  
157 orally swallowed immediate release tablet of tramadol. Patients with a variety of chronic  
158 painful conditions were studied in double-blind trials of one to three months duration.  
159 Average daily doses of approximately 250 mg of an orally swallowed immediate release  
160 tablet of tramadol in divided doses were generally comparable to five doses of  
161 acetaminophen 300 mg with codeine phosphate 30 mg daily, five doses of aspirin 325 mg  
162 with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with  
163 oxycodone hydrochloride 5 mg daily.

164 **Titration Trials**

165 In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day  
166 titration to a daily orally swallowed immediate release tablet of tramadol dose of 200 mg  
167 (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer  
168 discontinuations due to dizziness or vertigo than titration over only 4 days or no titration.

169 Figure 2: Protocol CAPSS -047 Time to Discontinuation Due to Nausea/Vomiting

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170

## 171 INDICATIONS AND USAGE

172 **TRADE NAME** is indicated for the management of moderate to moderately severe pain  
173 in adults.

## 174 CONTRAINDICATIONS

175 **TRADE NAME** should not be administered to patients who have previously  
176 demonstrated hypersensitivity to tramadol, any other component of this product or other  
177 opioids. **TRADE NAME** is contraindicated in any situation where other opioids are  
178 contraindicated, including acute intoxication with any of the following: alcohol,  
179 hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. **TRADE**  
180 **NAME** may worsen central nervous system and respiratory depression in these patients.

## 181 WARNINGS

### 182 Seizure Risk

183 **Seizures have been reported in patients receiving tramadol within the**  
184 **recommended dosage range. Spontaneous post-marketing reports indicate that**  
185 **seizure risk is increased with doses of tramadol above the recommended range.**  
186 **Concomitant use of **TRADE NAME** increases the seizure risk in patients taking:**

- 187 • **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- 188 • **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g.,**  
189 **cyclobenzaprine, promethazine, etc.), or**

- 190 • **Other Opioid drugs.**

191 Administration of **TRADE NAME** may enhance the seizure risk in patients taking:

- 192 • MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors),  
193 • Neuroleptics, or  
194 • Other drugs that reduce the seizure threshold.

195 Risk of convulsions may also increase in patients with epilepsy, those with a history  
196 of seizures, or in patients with a recognized risk for seizure (such as head trauma,  
197 metabolic disorders, alcohol and drug withdrawal, CNS infections). In **TRADE**  
198 **NAME** overdose, naloxone administration may increase the risk of seizure.

199 **Anaphylactoid Reactions**

200 Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving  
201 therapy with tramadol. When these events do occur it is often following the first dose.  
202 Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema,  
203 toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of  
204 anaphylactoid reactions to codeine and other opioids may be at increased risk and  
205 therefore should not receive **TRADE NAME** (see CONTRAINDICATIONS ).

206 **Respiratory Depression**

207 Administer **TRADE NAME** cautiously in patients at risk for respiratory depression. In  
208 these patients alternative non-opioid analgesics should be considered. When large doses  
209 of tramadol are administered with anesthetic medications or alcohol, respiratory  
210 depression may result. Respiratory depression should be treated as an overdose. If  
211 naloxone is to be administered, use cautiously because it may precipitate seizures (see  
212 WARNINGS , Seizure Risk and OVERDOSAGE ).

213 **Interaction With Central Nervous System (CNS) Depressants**

214 **TRADE NAME** should be used with caution and in reduced dosages when administered  
215 to patients receiving CNS depressants such as alcohol, other opioids, anesthetic agents,  
216 narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk  
217 of CNS and respiratory depression in these patients.

218

219 **Increased Intracranial Pressure or Head Trauma**

220 **TRADE NAME** should be used with caution in patients with increased intracranial  
221 pressure or head injury. The respiratory depressant effects of opioids include carbon  
222 dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be

223 markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from  
224 tramadol may obscure the existence, extent, or course of intracranial pathology.  
225 Clinicians should also maintain a high index of suspicion for adverse drug reaction when  
226 evaluating altered mental status in these patients if they are receiving TRADE NAME  
227 (See Respiratory Depression .)

#### 228 **Sensitivity to phenylketone**

229 Patients with a history of sensitivity to phenylketones may be at increased risk and  
230 therefore should not receive TRADE NAME.

#### 231 **Use in Ambulatory Patients**

232 TRADE NAME may impair the mental and or physical abilities required for the  
233 performance of potentially hazardous tasks such as driving a car or operating machinery.  
234 The patient using this drug should be cautioned accordingly.

#### 235 **Use With MAO Inhibitors And Serotonin Re-Uptake Inhibitors**

236 Use TRADE NAME with great caution in patients taking monoamine oxidase inhibitors.  
237 Animal studies have shown increased deaths with combined administration. Concomitant  
238 use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events,  
239 including seizure and serotonin syndrome.

#### 240 **Withdrawal**

241 Withdrawal symptoms may occur if TRADE NAME is discontinued abruptly. (See  
242 DRUG ABUSE AND DEPENDENCE .) These symptoms may include: anxiety,  
243 sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms,  
244 piloerection, and rarely hallucinations. Other symptoms that have been seen less  
245 frequently with reference listed drug discontinuation include: panic attacks, severe  
246 anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be  
247 relieved by tapering the medication.

#### 248 **Physical Dependence and Abuse**

249 TRADE NAME may induce psychic and physical dependence of the morphine-type ( $\mu$ -  
250 opioid) (see DRUG ABUSE AND DEPENDENCE ). TRADE NAME should not be used  
251 in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence  
252 in some patients who have been previously dependent on other opioids. Dependence and  
253 abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are  
254 not limited to those patients with prior history of opioid dependence.

#### 255 **Risk of Overdosage**

256 Serious potential consequences of overdosage with tramadol hydrochloride tablets are  
257 central nervous system depression, respiratory depression and death. In treating an  
258 overdose, primary attention should be given to maintaining adequate ventilation along  
259 with general supportive treatment (see OVERDOSAGE ).

## 260 **PRECAUTIONS**

### 261 **Acute Abdominal Conditions**

262 The administration of TRADE NAME may complicate the clinical assessment of patients  
263 with acute abdominal conditions.

### 264 **Use in Renal and Hepatic Disease**

265 Impaired renal function results in a decreased rate and extent of excretion of tramadol and  
266 its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min,  
267 dosing reduction is recommended (see DOSAGE AND ADMINISTRATION ).  
268 Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the  
269 liver. In cirrhotic patients, dosing reduction is recommended (see DOSAGE AND  
270 ADMINISTRATION ).

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

### 273 **Information for Patients**

- 274 • TRADE NAME may impair mental or physical abilities required for the performance  
275 of potentially hazardous tasks such as driving a car or operating machinery.
  - 276 • TRADE NAME should not be taken with alcohol containing beverages.
  - 277 • TRADE NAME should be used with caution when taking medications such as  
278 tranquilizers, hypnotics or other opiate containing analgesics.
  - 279 • Female patients should be instructed to inform the physician if they are pregnant,  
280 think they might become pregnant, or are trying to become pregnant (see  
281 PRECAUTIONS , Labor and Delivery ).
  - 282 • The patient should understand the single-dose and 24-hour dose limit and the time  
283 interval between doses, since exceeding these recommendations can result in  
284 respiratory depression, seizures and death.
  - 285 • To open the blister pack, peel back the foil on the blister. Do not push tablet through  
286 the foil. Remove the tablet and place it in the mouth, where it will dissolve in  
287 seconds and then be swallowed with the saliva.
  - 288 • Tablet may be taken with or without water.
  - 289 • Do NOT chew, break, or split the tablet.
-

- 290 • Phenylketonurics: TRADE NAME contains phenylalanine.

291 **Drug Interactions**

292 In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated  
293 metabolism of other drugs when tramadol is administered concomitantly at therapeutic  
294 doses. Tramadol does not appear to induce its own metabolism in humans, since observed  
295 maximal plasma concentrations after multiple oral doses are higher than expected based  
296 on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways  
297 measured in animals.

298 *Use With Carbamazepine*

299 Patients taking **carbamazepine** may have a significantly reduced analgesic effect of  
300 tramadol. Because carbamazepine increases tramadol metabolism and because of the  
301 seizure risk associated with tramadol, concomitant administration of TRADE NAME and  
302 carbamazepine is not recommended.

303 *Use With Quinidine*

304 Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of the  
305 isoenzyme, so that concomitant administration of quinidine and tramadol results in  
306 increased concentrations of tramadol and reduced concentrations of M1. The clinical  
307 consequences of these findings are unknown. In vitro drug interaction studies in human  
308 liver microsomes indicate that tramadol has no effect on quinidine metabolism.

309 *Use With Inhibitors of CYP2D6*

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

313

314

315 *Use With Cimetidine*

316 Concomitant administration with **cimetidine** does not result in clinically significant  
317 changes in tramadol pharmacokinetics. Therefore, no alteration of the TRADE NAME  
318 dosage regimen is recommended.

319 *Use With MAO Inhibitors*

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320 Interactions with **MAO Inhibitors** , due to interference with detoxification mechanisms,  
321 have been reported for some centrally acting drugs (see WARNINGS , Use With MAO  
322 Inhibitors).

323 *Use With Digoxin and Warfarin*

324 Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and  
325 alteration of warfarin effect, including elevation of prothrombin times.

### 326 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

327 A slight, but statistically significant, increase in two common murine tumors, pulmonary  
328 and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice.  
329 Mice were dosed orally up to 30 mg/kg (90 mg/m<sup>2</sup> or 0.36 times the maximum daily  
330 human dosage of 246 mg/m<sup>2</sup>) for approximately two years, although the study was not  
331 done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in  
332 humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to  
333 30 mg/kg, 180 mg/m<sup>2</sup>, or 0.73 times the maximum daily human dosage).

334 Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal  
335 activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the  
336 absence of metabolic activation), dominant lethal mutation tests in mice, chromosome  
337 aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and  
338 Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic  
339 activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the  
340 weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk  
341 to humans.

342 No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg  
343 (300 mg/m<sup>2</sup>) in male rats and 75 mg/kg (450 mg/m<sup>2</sup>) in female rats. These dosages are  
344 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m<sup>2</sup>, respectively.

### 345 **Pregnancy, Teratogenic Effects: Pregnancy Category C .**

346 Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or  
347 360 mg/m<sup>2</sup>), rats ( $\geq 25$  mg/kg or 150 mg/m<sup>2</sup>) and rabbits ( $\geq 75$  mg/kg or 900 mg/m<sup>2</sup>)  
348 at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages  
349 on a mg/m<sup>2</sup> basis are 1.4,  $\geq 0.6$ , and  $\geq 3.6$  times the maximum daily human dosage  
350 (246 mg/m<sup>2</sup>) for mouse, rat and rabbit, respectively.

351 No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg  
352 or 420 mg/m<sup>2</sup>), rats (up to 80 mg/kg or 480 mg/m<sup>2</sup>) or rabbits (up to 300 mg/kg or

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353 3600 mg/m<sup>2</sup>) treated with tramadol by various routes. Embryo and fetal toxicity  
354 consisted primarily of decreased fetal weights, skeletal ossification and increased  
355 supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or  
356 behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo  
357 and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m<sup>2</sup>), a  
358 dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for  
359 mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage  
360 (246 mg/m<sup>2</sup>), respectively.

#### 361 *Non-teratogenic Effects*

362 Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving  
363 oral (gavage) dose levels of 50 mg/kg (300 mg/m<sup>2</sup> or 1.2 times the maximum daily  
364 human tramadol dosage) or greater had decreased weights, and pup survival was  
365 decreased early in lactation at 80 mg/kg (480 mg/m<sup>2</sup> or 1.9 and higher the maximum  
366 daily human dose).

367 There are no adequate and well-controlled studies in pregnant women. Tramadol should  
368 be used during pregnancy only if the potential benefit justifies the potential risk to the  
369 fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have  
370 been reported during post-marketing.

#### 371 **Labor and Delivery**

372 **TRADE NAME** should not be used in pregnant women prior to or during labor unless the  
373 potential benefits outweigh the risks. Safe use in pregnancy has not been established.  
374 Chronic use during pregnancy may lead to physical dependence and post-partum  
375 withdrawal symptoms in the newborn (see DRUG ABUSE AND DEPENDENCE ).  
376 Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the  
377 umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol  
378 during labor.

379 The effect of tramadol if any, on the later growth, development, and functional  
380 maturation of the child is unknown.

#### 381 **Nursing Mothers**

382 **TRADE NAME** is not recommended for obstetrical preoperative medication or for post-  
383 delivery analgesia in nursing mothers because its safety in infants and newborns has not  
384 been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in  
385 breast milk within 16 hours postdose was 100 µg of tramadol (0.1% of the maternal dose)  
386 and 27 µg of M1.

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387 **Pediatric Use**

388 The safety and efficacy of TRADE NAME in patients under 16 years of age have not  
389 been established. The use of TRADE NAME in the pediatric population is not  
390 recommended.

391 **Geriatric Use**

392 In general, dose selection for an elderly patient should be cautious, usually starting at the  
393 low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal  
394 or cardiac function and of concomitant disease or other drug therapy. In patients over  
395 75 years of age, daily doses in excess of 300 mg are not recommended (see CLINICAL  
396 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

397 A total of 455 elderly (65 years of age or older) subjects were exposed to tramadol in  
398 controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

399 In studies including geriatric patients, treatment-limiting adverse events were higher in  
400 subjects over 75 years of age compared to those under 65 years of age. Specifically, 30%  
401 of those over 75 years of age had gastrointestinal treatment-limiting adverse events  
402 compared to 17% of those under 65 years of age. Constipation resulted in discontinuation  
403 of treatment in 10% of those over 75.

404 **ADVERSE REACTIONS**

405 An orally swallowed immediate release tablet of tramadol was administered to 550  
406 patients during the double-blind or open-label extension periods in U.S. studies of  
407 chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 2  
408 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the  
409 most frequent reactions (5% or more by 7 days). The most frequently reported events  
410 were in the central nervous system and gastrointestinal system. Although the reactions  
411 listed in the table are felt to be probably related to tramadol administration, the reported  
412 rates also include some events that may have been due to underlying disease or  
413 concomitant medication. The overall incidence rates of adverse experiences in these trials  
414 were similar for tramadol and the active control groups, acetaminophen 300 mg with  
415 codeine phosphate 30 mg, and aspirin 325 mg with codeine phosphate 30 mg, however,  
416 the rates of withdrawals due to adverse events appeared to be higher in the tramadol  
417 groups.

418 Table 2: Cumulative Incidence of Adverse Reactions for Tramadol Hydrochloride in  
419 Chronic Trials of Nonmalignant Pain (N = 427)

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	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” <sup>1</sup>	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

<sup>1</sup> “CNS Stimulation” is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

420

421 *Incidence 1% to less than 5%, possibly causally related:*

422 the following lists adverse reactions that occurred with an incidence of 1% to less than  
423 5% in clinical trials, and for which the possibility of a causal relationship with tramadol  
424 exists.

425 **Body as a Whole:** Malaise.

426 **Cardiovascular:** Vasodilation.

427 **Central Nervous System:** Anxiety, Confusion, Coordination disturbance, Euphoria,  
428 Miosis, Nervousness, Sleep disorder.

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

430 **Musculoskeletal:** Hypertonia.

431 **Skin:** Rash.

432 **Special Senses:** Visual disturbance.

433 **Urogenital:** Menopausal symptoms, Urinary frequency, Urinary retention.

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

437 **Body as a Whole:** Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal  
438 tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever,  
439 shivering, tremor, agitation, diaphoresis, seizures and coma).

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

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

444 **Respiratory:** Dyspnea.

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

446 **Special Senses:** Dysgeusia.

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

448 *Other adverse experiences, causal relationship unknown:* A variety of other adverse  
449 events were reported infrequently in patients taking tramadol during clinical trials and/or  
450 reported in post-marketing experience. A causal relationship between tramadol and these  
451 events has not been determined. However, the most significant events are listed below as  
452 alerting information to the physician.

453 **Cardiovascular:** Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia,  
454 Palpitations, Pulmonary edema, Pulmonary embolism.

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

456 **Gastrointestinal:** Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.

457 **Laboratory Abnormalities:** Creatinine increase, Elevated liver enzymes, Hemoglobin  
458 decrease, Proteinuria.

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

460 **DRUG ABUSE AND DEPENDENCE**

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461 **TRADE NAME** may induce psychic and physical dependence of the morphine-type ( $\mu$ -  
462 opioid). (See **WARNINGS** .) Dependence and abuse, including drug-seeking behavior  
463 and taking illicit actions to obtain the drug are not limited to those patients with prior  
464 history of opioid dependence. The risk in patients with substance abuse has been  
465 observed to be higher. Tramadol is associated with craving and tolerance development.  
466 Withdrawal symptoms may occur if **TRADE NAME** is discontinued abruptly. These  
467 symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors,  
468 diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. **Other**  
469 **symptoms that have been seen less frequently with reference listed drug discontinuation**  
470 **include: panic attacks, severe anxiety, and paresthesias.** Clinical experience suggests that  
471 withdrawal symptoms may be relieved by reinstatement of opioid therapy followed by a  
472 gradual, tapered dose reduction of the medication combined with symptomatic support.

### 473 **OVERDOSAGE**

474 Serious potential consequences of overdosage are respiratory depression, lethargy, coma,  
475 seizure, cardiac arrest and death. (See **WARNINGS** .) Fatalities have been reported in  
476 post marketing in association with both intentional and unintentional overdose with  
477 tramadol. In treating an overdose, primary attention should be given to maintaining  
478 adequate ventilation along with general supportive treatment. While naloxone will  
479 reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of  
480 seizures is also increased with naloxone administration. In animals convulsions following  
481 the administration of toxic doses of tramadol could be suppressed with barbiturates or  
482 benzodiazepines but were increased with naloxone. Naloxone administration did not  
483 change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in  
484 an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis  
485 period.

### 486 **DOSAGE AND ADMINISTRATION**

487 **Do NOT chew, break, or split the tablet.**

488 Adults (17 years of age and over)

489 For patients with moderate to moderately severe chronic pain not requiring rapid onset of  
490 analgesic effect, the tolerability of **Other symptoms that have been seen less frequently**  
491 **with reference listed drug discontinuation include: panic attacks, severe anxiety, and**  
492 **paresthesias.** can be improved by initiating therapy with a titration regimen. The total  
493 daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50

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494 mg q.i.d.). After titration, TRADE NAME 50 to 100 mg can be administered as needed  
495 for pain relief every 4 to 6 hours **not to exceed 400 mg/day**.

496 For the subset of patients for whom rapid onset of analgesic effect is required and for  
497 whom the benefits outweigh the risk of discontinuation due to adverse events associated  
498 with higher initial doses, TRADE NAME 50 mg to 100 mg can be administered as  
499 needed for pain relief every 4 to 6 hours, **not to exceed 400 mg per day**.

500 Place TRADE NAME tablet on the tongue until it completely disintegrates and then  
501 swallow it. It may take approximately one minute for the tablet to disintegrate on the  
502 tongue. Tablet may be taken with or without water.

### 503 Individualization of Dose

504 Good pain management practice dictates that the dose be individualized according to  
505 patient need using the lowest beneficial dose. Studies with tramadol in adults have shown  
506 that starting at the lowest possible dose and titrating upward will result in fewer  
507 discontinuations and increased tolerability.

508 In all patients with **creatinine clearance less than 30 mL/min**, it is recommended that  
509 the dosing interval of TRADE NAME be increased to 12 hours, with a maximum daily  
510 dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis,  
511 **dialysis patients** can receive their regular dose on the day of dialysis.

512 The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.

513 In general, dose selection for an elderly patient over 65 years old should be cautious,  
514 usually starting at the low end of the dosing range, reflecting the greater frequency of  
515 decreased hepatic, renal or cardiac function and of concomitant disease or other drug  
516 therapy. For elderly patients **over 75 years old**, total dose should not exceed 300 mg/day.

### 517 HOW SUPPLIED

518 TRADE NAME tramadol hydrochloride orally disintegrating tablets - 50 mg (white,  
519 tablet) debossed with "B" on one side and "50" on the other side.

520 30 tablets, 5 cards of 6 single dose units in child resistant blister packs.

521 Store at 25°C (77°F); excursions permitted to 15-30°C (59-89°F).

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/s/

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Sharon Hertz  
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