

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-745

LABELING

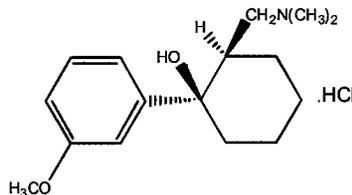
1
2
3
4

RYZOLT™
(tramadol hydrochloride extended-release tablets)

5
6

Description

7 **RYZOLT™ (tramadol hydrochloride extended-release tablets)** is a centrally acting analgesic
8 composed of a dual-matrix delivery system with both immediate-release and extended-release
9 characteristics. The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)
10 methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



12 $C_{16}H_{25}NO_2 \cdot HCl$

13
14 The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white
15 crystalline powder that is freely soluble in **water and ethanol**. **RYZOLT™ extended-release**
16 tablets are for oral administration and contain 100 mg, 200 mg or 300 mg of tramadol
17 hydrochloride. The tablets are white to off-white in color. The inactive ingredients in the tablet
18 are colloidal silicon dioxide, pregelatinized modified starch, hydrogenated vegetable oil,
19 magnesium stearate, polyvinyl acetate, povidone, sodium lauryl sulfate and xanthan gum.

20
21
22

Clinical Pharmacology

23
24

Mechanism of Action

25 **RYZOLT™ is a centrally acting synthetic opioid analgesic.** Although its mode of action is not
26 completely understood, at least two complementary mechanisms that demonstrate three different
27 types of activity appear applicable: binding of parent and M1 metabolite to μ -opioid receptors
and weak inhibition of reuptake of norepinephrine and serotonin.

28 Opioid activity is due to both low affinity binding of the parent compound and higher affinity
29 binding of the α -demethylated metabolite (M1) to μ -opioid receptors. In animal models, M1 is
30 up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -
31 opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist
32 naloxone in several animal tests. The relative contribution of both tramadol and M1 to human
33 analgesia is dependent upon the plasma concentrations of each compound.

34
35 Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have
36 some other opioid analgesics. These mechanisms may contribute independently to the overall
37 analgesic profile of tramadol.

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

43

44 **Pharmacokinetics**

45 The analgesic activity of tramadol hydrochloride is due to both parent drug and the M1
 46 metabolite (See **CLINICAL PHARMACOLOGY, Mechanism of Action**).

47 **RYZOLT™ is formulated as a racemate and both tramadol and M1 are detected in the**
 48 **circulation.**

49 The pharmacokinetics of tramadol and M1 are dose-proportional over a 100 to 300 mg dose range
 50 in healthy subjects.

51

52 **Absorption**

53 The median time to peak plasma concentrations of tramadol and M1 after multiple-dose
 54 **administration of RYZOLT™ 200 mg tablets** to healthy subjects are attained at about 4 h and 5 h,
 55 respectively (Table 1 and Figure 1).

56 The pharmacokinetic parameter values for **RYZOLT™ 200 mg administered once daily and**
 57 **tramadol immediate-release 50 mg administered every six hours** are provided in Table 1. The
 58 **relative bioavailability of a 200 mg RYZOLT™ tablet** compared to a 50 mg immediate-release
 59 tablet dosed every six hours was approximately 95% in healthy subjects.

60

61 **Table 1. Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=26).**

62

Pharmacokinetic Parameter	Tramadol		M1 Metabolite	
	RYZOLT™ 200 mg Tablet Once-Daily	Immediate- release tramadol 50 mg Tablet Every 6 Hours	RYZOLT™ 200 mg Tablet Once-Daily	Immediate- release tramadol 50 mg Tablet Every 6 Hours
AUC ₀₋₂₄ (ng·h/mL)	5991 (22)	6399 (28)	1361 (27)	1438 (23)
C _{max} (ng/mL)	345 (21)	423 (23)	71 (27)	79 (22)
C _{min} (ng/mL)	157 (31)	190 (34)	41 (30)	50 (29)
T _{max} (hr)*	4.0 (3.0 – 9.0)	1.0 (1.0 – 3.0)	5.0 (3.0 – 20)	1.5 (1.0 – 3.0)
Fluctuation (%)	77 (26)	91 (22)	53 (29)	49 (26)

63 *T_{max} is presented as Median (Range)

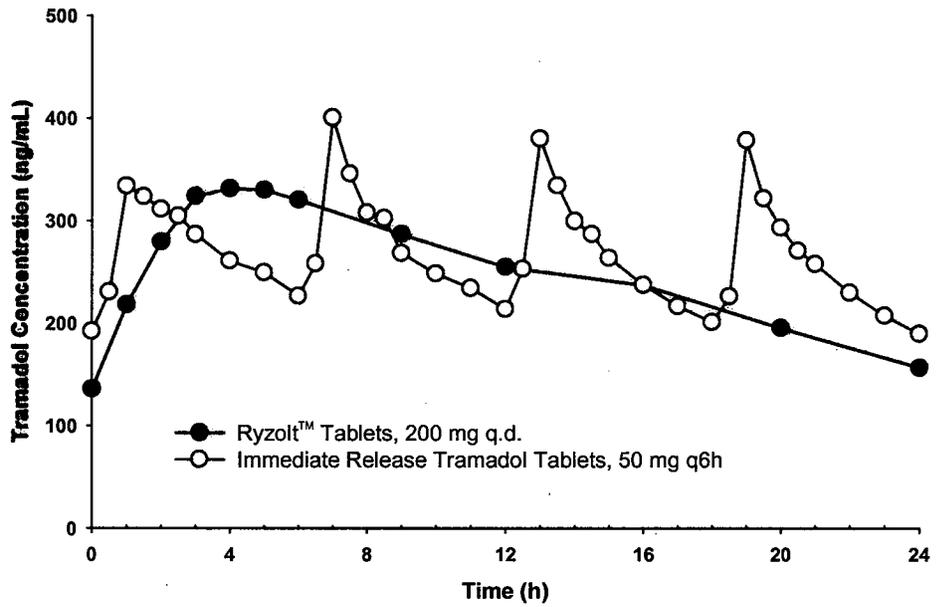
64

65 Steady-state plasma concentrations are reached within approximately 48 hours.

66

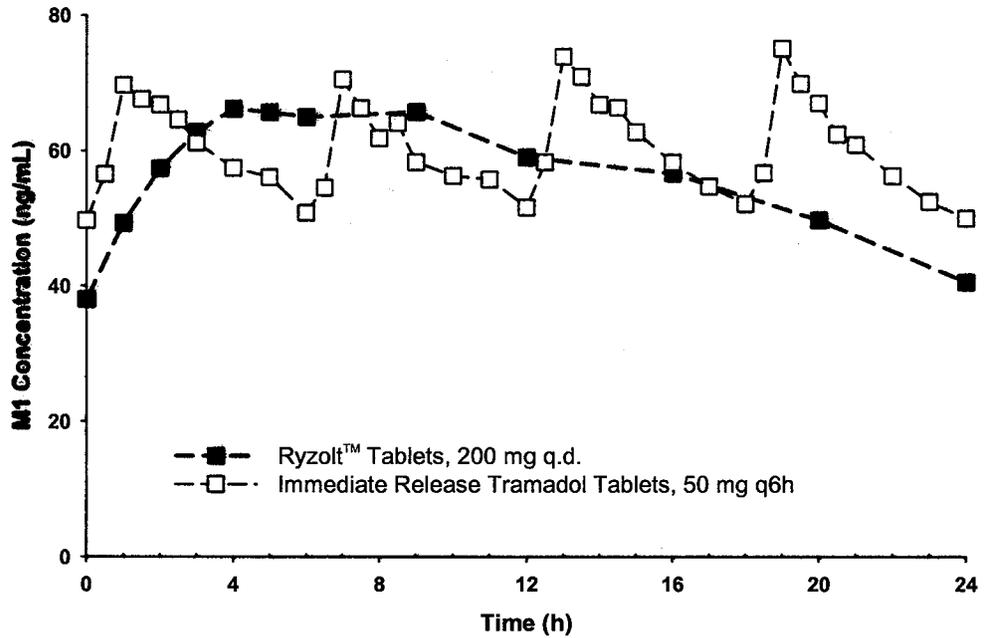
67
68
69

Figure 1. Mean Tramadol Plasma Concentrations at Steady State Following Five Days of Oral Administration of RYZOLT™ 200 mg Once Daily and Immediate-Release Tramadol 50 mg Every 6 Hours.



70
71
72
73
74

Figure 2. Mean M1 Plasma Concentrations at Steady State Following Five Days of Oral Administration of RYZOLT™ 200 mg Once Daily and Immediate-Release Tramadol 50 mg Every 6 Hours.



75
76

77

78 **Food Effect**

79 Co-administration with a high fat meal did not significantly affect AUC (overall exposure to
80 tramadol); however, C_{max} (peak plasma concentration) increased 67% following a single 300 mg
81 **tablet administration and 54% following a single 200 mg tablet administration. RYZOLT™** was
82 administered without regard to food in all clinical trials.

83

84 **Distribution**

85 The volume of distribution of tramadol is 2.6 and 2.9 L/kg in males and females, respectively,
86 following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is
87 approximately 20%. Protein binding also appears to be independent of concentration up to
88 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the
89 clinically relevant range.

90

91 **Metabolism**

92 Tramadol is extensively metabolized after oral administration. The major metabolic pathways
93 appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. *N*-
94 demethylation is mediated by CYP3A4 and CYP2B6. One metabolite (*O*-desmethyltramadol,
95 denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on
96 CYP2D6 and as such is subject to inhibition and polymorphism, which may affect the therapeutic
97 response (See **PRECAUTIONS - Drug Interactions**).

98

99 **Elimination**

100 Tramadol is eliminated primarily through metabolism by the liver and the metabolites are
101 eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as
102 unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted
103 **either as unidentified or as unextractable metabolites. After single administration of RYZOLT™**,
104 the mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are $6.5 \pm$
105 1.5 and 7.5 ± 1.4 hours, respectively.

106

107 **Special Populations**

108

109 **Renal Impairment**

110 Impaired renal function results in a decreased rate and extent of excretion of tramadol and its
111 active metabolite, M1 in patients taking an immediate-release formulation of tramadol.
112 **RYZOLT™ has not been studied in patients with renal impairment.** The limited availability of
113 **dose strengths and once daily dosing of RYZOLT™** do not permit the dosing flexibility required
114 for safe use in patients with severe renal impairment. **Therefore, RYZOLT™ should not be used**
115 in patients with severe renal impairment (creatinine clearance less than 30 mL/min) (See
116 **WARNINGS, Use in Renal and Hepatic Disease and DOSAGE AND ADMINISTRATION**).
117 The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of
118 the administered dose.

119

120 **Hepatic Impairment**

121 The metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver,
122 resulting in both a larger area under the concentration time curve (AUC) for tramadol and longer
123 mean tramadol and M1 elimination half-lives (13 hours for tramadol and 19 hours for M1) after
124 **the administration of tramadol immediate-release tablets. RYZOLT™ has not been studied in**
125 patients with hepatic impairment. The limited availability of dose strengths and once daily dosing
126 **of RYZOLT™ do not permit the dosing flexibility** required for safe use in patients with hepatic
127 impairment. Therefore, **RYZOLT™ should not be used in patients** with hepatic impairment (see
128 **WARNINGS, Use in Renal and Hepatic Disease and DOSAGE AND ADMINISTRATION**).

129

130 **Geriatric Patients**

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

137

138 **Gender**

139 Following a 100 mg IV dose of tramadol, plasma clearance was 6.4 mL/min/kg in males and 5.7
140 mL/min/kg in females. Following a single oral dose of immediate-release tramadol, and after
141 adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35%
142 higher area under the concentration-time curve compared to males. The clinical significance of
143 this difference is unknown.

144

145 **Drug Interactions**

146 The formation of the active metabolite of tramadol, M1, is mediated by CYP2D6, a polymorphic
147 enzyme. Approximately 7% of the population has reduced activity of CYP2D6. These individuals
148 are "poor metabolizers" of debrisoquine, dextromethorphan and tricyclic antidepressants, among
149 other drugs. In studies in healthy subjects administered immediate-release tramadol products,
150 concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus
151 "extensive metabolizers", while M1 concentrations were 40% lower. *In vitro* drug interaction
152 studies in human liver microsomes indicate that inhibitors of CYP2D6 (amitriptyline, quinidine
153 and fluoxetine and its metabolite norfluoxetine,) inhibit the metabolism of tramadol to various
154 degrees, suggesting that concomitant administration of these compounds could result in increases
155 in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact
156 of these alterations in terms of either efficacy or safety is unknown.

157 Tramadol is also metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as
158 ketoconazole and erythromycin, or inducers, **such as rifampin and St. John's Wort, with**
159 **RYZOLT™ may affect the metabolism of tramadol** leading to altered tramadol exposure (see
160 **PRECAUTIONS**).

161

162 *Quinidine*

163 Quinidine is a selective inhibitor of CYP2D6, so that concomitant administration of quinidine and
164 **RYZOLT™ may result in increased concentrations** of tramadol and reduced concentrations of
165 M1. The clinical consequences of these findings are unknown (see **PRECAUTIONS**). *In vitro*

166 drug interaction studies in human liver microsomes indicate that tramadol has no effect on
167 quinidine metabolism.

168

169 *Carbamazepine*

170 Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking
171 carbamazepine may have a significantly reduced analgesic effect of tramadol. Because of the
172 seizure risk associated with tramadol, **concomitant administration of RYZOLT™ and**
173 carbamazepine is not recommended (see **PRECAUTIONS**).

174

175 *Cimetidine*

176 Concomitant administration of tramadol immediate-release tablets with cimetidine does not result
177 in clinically significant changes in tramadol **pharmacokinetics**. **No alteration of the RYZOLT™**
178 dosage regimen with cimetidine is recommended.

179

180

Clinical Studies

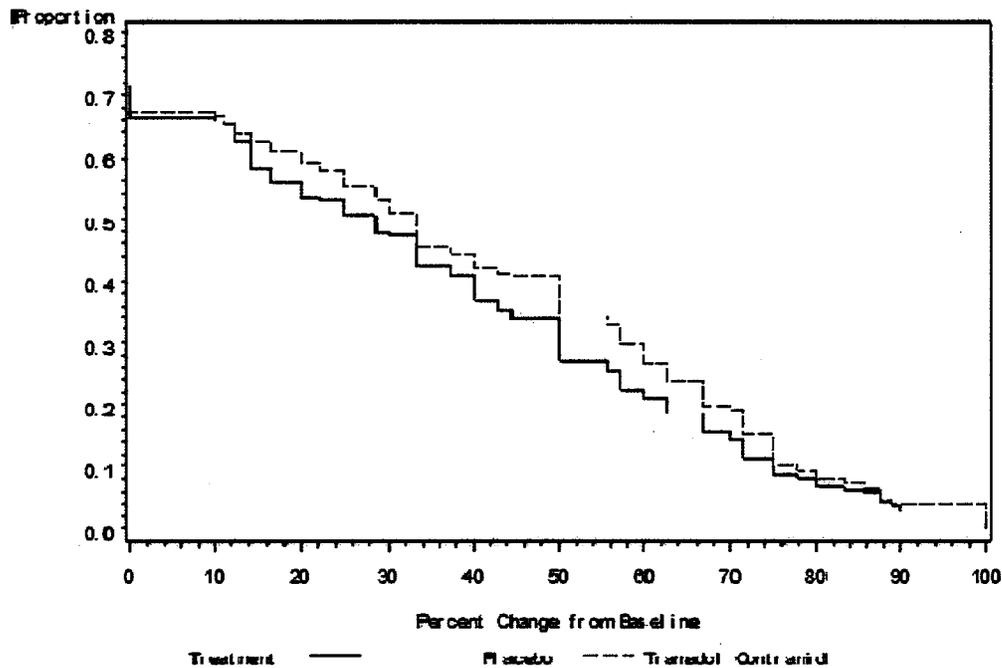
181

182 **RYZOLT™ was studied in four 12-week, randomized, double-blind, controlled studies in**
183 **patients with moderate to severe pain due to osteoarthritis. Efficacy was demonstrated in one**
184 **double-blind, placebo-controlled, randomized withdrawal design study. In this study, patients**
185 **who experienced a reduction of pain and were able to tolerate RYZOLT™ during an open-label**
186 **titration period, were then randomized to RYZOLT™ or to placebo for 12 weeks. Sixty-five**
187 **percent of patients were able to successfully titrate onto RYZOLT™. After a washout, patients**
188 **randomized to RYZOLT™ were titrated to 200 mg or 300 mg of RYZOLT™ based on**
189 **tolerability and remained on that dose for the following 12-week period. Approximately 24% of**
190 **patients discontinued during the randomized period of the study, with more patients discontinuing**
191 **from the RYZOLT™ arm than the placebo arm due to adverse events (10% vs. 5%, respectively)**
192 **and more patients discontinuing from the placebo arm than the RYZOLT™ arm due to lack of**
193 **efficacy (10% vs. 8%, respectively). Patients treated with RYZOLT™ demonstrated a greater**
194 **improvement in pain intensity, measured on an 11-point numerical rating scale, at the end of**
195 **treatment compared to patients randomized to placebo. Figure 3 shows the fraction of patients**
196 **achieving various degree of improvement in pain from baseline to the end of treatment (week 12).**
197 **The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are**
198 **also included at every level of improvement below 50%. Patients who did not complete the study**
199 **were assigned 0% improvement.**

Appears This Way
On Original

200

201 **Figure 3. Proportion of Patients Achieving Various Levels of Pain Relief as Measured by**
202 **12-Week Pain Intensity.**



203

204

205

206

Indications and Usage

207

208 **RYZOLT™ is indicated for the management of moderate to moderately severe chronic pain in**
209 **adults who require around-the-clock treatment of their pain for an extended period of time.**

210

211

212

Contraindications

213

214 **RYZOLT™ should not be administered to patients who have previously demonstrated**
215 **hypersensitivity to tramadol, any other component of this product or opioids.**

216 **RYZOLT™ is contraindicated in patients with significant respiratory depression in unmonitored**
217 **settings or the absence of resuscitative equipment. RYZOLT™ is also contraindicated in**
218 **patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the**
219 **absence of resuscitative equipment.**

220

221

Warnings

222

223

224 Seizure Risk

225 Seizures have been reported in patients receiving tramadol hydrochloride within the
226 recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk
227 is increased with doses above the recommended range. Concomitant use of tramadol
228 hydrochloride increases the seizure risk in patients taking:

- 229 ▪ Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),
- 230 ▪ Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine,
231 promethazine, etc.), or
- 232 ▪ Other opioids.

233 **Administration of RYZOLT™ may enhance the seizure risk in patients taking:**

- 234 ▪ Monoamine Oxidase (MAO) inhibitors (**See also WARNINGS – Use with MAO**
235 **Inhibitors and Serotonin Re-uptake Inhibitors**),
- 236 ▪ Neuroleptics, or
- 237 ▪ Other drugs that reduce the seizure threshold.

238 Risk of convulsions may also be increased in patients with epilepsy, those with a history of
239 seizures, or in patients with a recognized risk for seizure (such as head trauma, certain
240 metabolic disorders, alcohol and drug withdrawal and CNS infections). In tramadol
241 overdose, naloxone administration may increase the risk of seizures.

242

243 Suicide Risk

244 Do not prescribe RYZOLT™ for patients who are suicidal or addiction-prone. Prescribe
245 RYZOLT™ with caution for patients taking tranquilizers or antidepressant drugs and for patients
246 who use alcohol in excess. Serious potential consequences of overdosage with RYZOLT™ are
247 central nervous system depression, respiratory depression and death. In treating an overdose,
248 primary attention should be given to maintaining adequate ventilation along with general
249 supportive treatment (see OVERDOSAGE).

250

251 Serotonin Syndrome risk

252 The development of a potentially life-threatening serotonin syndrome may occur with the
253 use of tramadol products, including RYZOLT™, particularly with concomitant use of
254 serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, and triptans, with drugs which
255 impair metabolism of serotonin (including MAOIs), and with drugs which impair
256 metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur within the
257 recommended dose (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

258 Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations,
259 coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia),
260 neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal
261 symptoms (e.g., nausea, vomiting, diarrhea).

262 Tramadol products in excessive doses, either alone or in combination with other Central Nervous
263 System (CNS) depressants, including alcohol, are a major cause of drug-related deaths. Fatalities
264 within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses
265 higher than those recommended by the physician. The judicious prescribing of tramadol is
266 essential to the safe use of this drug. With patients who are depressed or suicidal, consideration

267 should be given to the use of non-narcotic analgesics. Patients should be cautioned about the
268 concomitant use of tramadol products and alcohol because of potentially serious CNS-additive
269 effects of these agents. Because of its added depressant effects, tramadol should be prescribed
270 with caution for those patients whose medical condition requires the concomitant administration
271 of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs.
272 Patients should be advised of the additive depressant effects of these combinations.

273 Many of the tramadol-related deaths have occurred in patients with previous histories of
274 emotional disturbances or suicidal ideation or attempts as well as histories of misuse of
275 tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence
276 of the accidental ingestion of excessive quantities of tramadol alone or in combination with other
277 drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their
278 physician.

279

280 **Anaphylactoid Reactions**

281 Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy
282 with tramadol. When these events do occur, it is often following the first dose. Other reported
283 allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis
284 and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to other
285 **opioids may be at increased risk and therefore should not receive RYZOLT™ (See**
286 **CONTRAINDICATIONS).**

287

288 **Respiratory Depression**

289 **RYZOLT™** should be administered cautiously in patients at risk for respiratory depression. In
290 these patients, alternative non-opioid analgesics should be considered. When large doses of
291 tramadol are administered with anesthetic medications or alcohol, respiratory depression may
292 result. Respiratory depression should be treated as an overdose. If naloxone is to be administered,
293 use cautiously because it may precipitate seizures (See **WARNINGS, Seizure Risk and**
294 **OVERDOSAGE).**

295

296 **Interaction with Central Nervous System (CNS) Depressants**

297 **RYZOLT™** should be used with caution and in reduced dosages when administered to patients
298 receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines,
299 tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory
300 depression in these patients.

301

302 **Increased Intracranial Pressure or Head Trauma**

303 **RYZOLT™** should be used with caution in patients with increased intracranial pressure or head
304 injury. The respiratory depressant effects of opioids include carbon dioxide retention and
305 secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these
306 patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence,
307 extent, or course of intracranial pathology. Clinicians should also maintain a high index of
308 suspicion for adverse drug reaction when evaluating altered mental status in these patients if they
309 **are receiving RYZOLT™ (See Respiratory Depression).**

310

311 **Use in Ambulatory Patients**
312 RYZOLT™ may impair the mental and physical abilities required for the performance of
313 potentially hazardous tasks such as driving a car or operating machinery. Patients using this drug
314 should be cautioned accordingly.

315

316 **Use with MAO Inhibitors and Serotonin Re-uptake Inhibitors**
317 RYZOLT™ should be used with great caution in patients taking MAO inhibitors. Animal studies
318 have shown increased deaths with combined administration of tramadol and MAO inhibitors.
319 Concomitant use of tramadol products with MAO inhibitors or SSRIs increases the risk of
320 adverse events, including seizure and serotonin syndrome.

321

322 **Withdrawal**

323 Withdrawal symptoms may occur if RYZOLT™ is discontinued abruptly. These symptoms may
324 include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory
325 symptoms, piloerection, and rarely hallucinations.

326

327 In a 12 week study, 325 patients were followed for 3 and 7 days after discontinuation of treatment
328 with RYZOLT™. The majority of reported post-treatment adverse events including withdrawal
329 symptoms were mild to moderate in nature. Onset of the post-treatment adverse events occurred
330 more frequently within the first three days after treatment was stopped. Less than 1% of patients
331 taking RYZOLT™ met the DSM-IV criteria for a diagnosis of opioid withdrawal.

332 Clinical experience suggests that signs and symptoms of withdrawal may be reduced by tapering
333 medication when discontinuing tramadol therapy.

334

335 **Misuse, Abuse and Diversion of Opioids**

336 Tramadol is an opioid agonist of the morphine type. Such drugs are sought by drug abusers and
337 people with addiction disorders and are subject to criminal diversion.

338 Like other opioid agonists, legal or illicit, tramadol can be abused. This should be considered
339 when prescribing or dispensing RYZOLT™ in situations where the healthcare professional is
340 concerned about a risk of misuse, abuse, or diversion.

341 RYZOLT™ could be abused by breaking, crushing, chewing, or dissolving the product which can
342 result in the uncontrolled delivery of the opioid, and as a consequence poses a significant risk of
343 overdose and death.

344 Concerns about abuse, addiction, and diversion should not prevent the proper management of
345 pain.

346

347 Healthcare professionals should contact their State Professional Licensing Board or State
348 Controlled Substances Authority for information on how to prevent and detect abuse or diversion
349 of this product.

350

351 **Interactions with Alcohol and Drugs of Abuse**

352 Tramadol may be expected to have additive effects when used in conjunction with alcohol, other
353 opioids or drugs, whether legal or illicit, which cause central nervous system depression.

354

355

356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402

DRUG ABUSE AND ADDICTION

Abuse

RYZOLT™ is a mu-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Concerns about abuse and addiction should not prevent the proper management of pain. However all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated **“loss”** of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). **“Doctor shopping” to obtain additional prescriptions** is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with **other psychoactive substances. RYZOLT™, like other opioids,** may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

RYZOLT™ is intended for oral use only. The crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist.

403 The opioid abstinence or withdrawal syndrome is characterized by some or all of the following:
404 restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other
405 symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness,
406 abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure,
407 respiratory rate, or heart rate. Generally, tolerance and/or withdrawal are more likely to occur the
408 longer a patient is on continuous opioid therapy.

411 **Risk of Overdosage**

412 Serious potential consequences of **overdosage with RYZOLT™** are central nervous system
413 depression, respiratory depression and death. In treating an overdose, primary attention should be
414 given to maintaining adequate ventilation along with general supportive treatment (See
415 **OVERDOSAGE**).

417 **Precautions**

419 **Acute Abdominal Conditions**

420 The administration of **RYZOLT™** may complicate the clinical assessment of patients with acute
421 abdominal conditions.

423 **Use in Renal and Hepatic Disease**

424 Impaired renal function results in a decreased rate and extent of excretion of tramadol and its
425 active metabolite, M1 in patients taking an immediate-release formulation of tramadol.

426 **RYZOLT™ has not been studied in patients with renal impairment.** The limited availability of
427 **dose strengths and once daily dosing of RYZOLT™** do not permit the dosing flexibility required
428 for safe use in patients with severe renal impairment. **Therefore, RYZOLT™ should not be used**
429 **in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE**
430 **AND ADMINISTRATION).**

432 The metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver.

433 **RYZOLT™ has not been studied in patients with hepatic impairment.** The limited availability of
434 **dose strengths and once daily dosing of RYZOLT™** do not permit the dosing flexibility required
435 for safe use in patients with hepatic impairment. **Therefore, RYZOLT™ should not be used in**
436 **patients with hepatic impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND**
437 **ADMINISTRATION).**

440 **Information for Patients**

442 **Patients should be instructed that:**

- 443 ■ **RYZOLT™** is for oral use only and should be swallowed whole with a sufficient quantity of
444 liquid and not split, chewed, dissolved or crushed.
- 445 ■ **RYZOLT™ may cause seizures and/or serotonin syndrome with concomitant use of**
446 **serotonergic agents (including SSRIs, SNRIs and triptans) or drugs that significantly reduce**
447 **the metabolic clearance of tramadol.**

- 448 ▪ **RYZOLT™** should be taken once daily, at approximately the same time every day and that
449 exceeding these instructions can result in respiratory depression, seizures or death.
- 450 ▪ **RYZOLT™** should not be taken in doses exceeding the maximum recommended daily dose
451 as exceeding these recommendations can result in respiratory depression, seizures or even
452 death (**See Dosage and Administration**)
- 453 ▪ **RYZOLT™** may impair the mental and physical abilities required for the performance of
454 potentially hazardous tasks such as driving a car or operating machinery. Patients using this
455 drug should be cautioned accordingly.
- 456 ▪ **RYZOLT™** should not be taken with alcohol-containing beverages.
- 457 ▪ **RYZOLT™** should be used with caution when taking medications such as tranquilizers,
458 hypnotics or other opiate containing analgesics.
- 459 ▪ Female patients should be instructed to inform the physician if they are pregnant, think they
460 might become pregnant, or are trying to become pregnant (**See PRECAUTIONS - Pregnancy**
461 **and Labor and Delivery**).
- 462 ▪ Clinical experience suggests that signs and symptoms of withdrawal may be reduced by
463 tapering medication when discontinuing tramadol therapy.
- 464 ▪ **Patients should be informed to keep RYZOLT™ out of reach of children.**

465

466 **Use in Drug and Alcohol Addiction**

467 **RYZOLT™ is an opioid** with no approved use for the management of addictive disorders. Its
468 proper usage in individuals with drug or alcohol dependence, either active or in remission is for
469 the management of pain requiring opioid analgesia.

470

471 **Drug Interactions**

472 *CYP2D6 and CYP3A4 Inhibitors:* Concomitant administration of CYP2D6 and/or CYP3A4
473 inhibitors (**see CLINICAL PHARMACOLOGY, Pharmacokinetics**), such as quinidine,
474 fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and
475 erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the
476 risk for serious adverse events including seizures and serotonin syndrome.

477 *Serotonergic Drugs:* There have been postmarketing reports of serotonin syndrome with use of
478 tramadol and SSRIs/SNRIs or MAOIs and α 2-adrenergic blockers. Caution is advised when
479 **RYZOLT™ is coadministered with other drugs that** may affect the serotonergic neurotransmitter
480 systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-
481 **selective MAOI**), lithium, or St. John's Wort. **If concomitant treatment of RYZOLT™ with a**
482 **drug affecting the serotonergic neurotransmitter system is clinically warranted, careful**
483 **observation of the patient is advised, particularly during treatment initiation and dose increases**
484 **(see WARNINGS, Serotonin Syndrome).**

485 *Triptans:* Based on the mechanism of action of tramadol and the potential for serotonin
486 **syndrome, caution is advised when RYZOLT™ is coadministered with a triptan.** If concomitant
487 **treatment of RYZOLT™ with a triptan is clinically warranted, careful observation of the patient**
488 **is advised, particularly during treatment initiation and dose increases (see WARNINGS,**
489 **Serotonin Syndrome).**

490

491 **Use with Carbamazepine**

492 Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic
493 effect. Because carbamazepine increases tramadol metabolism and because of the seizure risk
494 **associated with tramadol, concomitant administration of RYZOLT™** and carbamazepine is not
495 recommended.

496

497 **Use with Quinidine**

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

503

504 **Use with Digoxin and Warfarin**

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

507

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

509 **RYZOLT™ should be used with caution and in reduced dosages** when administered to patients
510 receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines,
511 **tranquilizers or sedative hypnotics. RYZOLT™** increases the risk of CNS and respiratory
512 depression in these patients.

513

514 **Potential of Other Drugs to Affect Tramadol**

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

518 Tramadol is partially metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as
519 ketoconazole and erythromycin, or inducers, **such as rifampin and St. John's Wort, with**
520 **RYZOLT™** may affect the metabolism of tramadol leading to altered tramadol exposure.

521

522 **Potential for Tramadol to Affect Other Drugs**

523 *In vitro* studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of
524 other drugs when administered concomitantly at therapeutic doses. Tramadol is a mild inducer of
525 selected drug metabolism pathways measured in animals.

526

527 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

528 A slight, but statistically significant increase in two common murine tumors, pulmonary and
529 hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were
530 dosed orally up to 30 mg/kg (90 mg/m² or 0.5 times the maximum daily human dosage of 185
531 mg/m²) for approximately two years, although the study was not done with the Maximum
532 Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred
533 in a rat carcinogenicity study (dosing orally up to 30 mg/kg - 180 mg/m² equal to the maximum
534 daily human dosage of tramadol).

535 Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation
536 test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic
537 activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese
538 hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Positive mutagenic
539 results occurred in the presence of metabolic activation in the mouse lymphoma assay and
540 micronucleus test in rats. Relevance of the finding in humans is unknown.

541 No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m²)
542 in male rats and 75 mg/kg (450 mg/m²) in female rats. These dosages are 1.6 and 2.4 times the
543 maximum daily human dosage of 185 mg/m², respectively.

544

545

546 **Pregnancy**

547 **Teratogenic Effects: Pregnancy Category C**

548 Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m²),
549 rats (≥25 mg/kg or 150 mg/m²) and rabbits (≥75mg/kg or 900 mg/m²) at maternally toxic
550 dosages, but was not teratogenic at these dose levels. These dosages on an mg/m² basis are 1.9,
551 0.8 and 4.9 times the maximum daily human dosage (185 mg/m²) for mouse, rat and rabbit,
552 respectively.

553 No drug related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420
554 mg/m²), rats (up to 80 mg/kg or 480 mg/m²) or rabbits (up to 300 mg/kg or 3600 mg/m²) treated
555 with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal
556 weights, skeletal ossification and increased supernumerary ribs in maternally toxic dose levels.
557 Transient delays in developmental or behavioral parameters were also seen in pups from rat dams
558 allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg
559 (3600 mg/m²), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed
560 for mouse, rat and rabbit are 2.2, 2.6 and 19.4 times the maximum daily human dosage (185
561 mg/m²), respectively.

562

563 **Non-teratogenic Effects**

564 Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral
565 (gavage) dose levels of 50 mg/kg (300 mg/m² or 1.6 times the maximum daily human RYZOLT
566 dosage) or greater had decreased weights, and pup survival was decreased early in lactation at
567 80 mg/kg (480 mg/m² or 2.6 times the maximum daily human dose).

568 **There are no adequate and well-controlled studies in pregnant women. RYZOLT™ should be**
569 **used during pregnancy only if the potential benefit justifies the potential risk to the fetus.**
570 Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported
571 during post-marketing surveillance of tramadol immediate-release products.

572

573 **Labor and Delivery**

574 RYZOLT™ should not be used in pregnant women prior to or during labor unless the potential
575 benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during
576 pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the
577 newborn (See **DRUG ABUSE AND ADDICTION**). Tramadol has been shown to cross the
578 placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins
579 was 0.83 for 40 women given tramadol during labor.

580 **The effect of RYZOLT™, if any, on the later growth, development and functional maturation of**
581 **the child is unknown.**

582

583 **Nursing Mother**

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

588

589 **Pediatric Use**

590 The safety and efficacy of RYZOLT™ in patients under 16 years of age has not been established.

591 **The use of RYZOLT™ in the pediatric population is not recommended.**

592

593 **Geriatric Use**

594 In general, caution should be used when selecting the dose for an elderly patient. Usually, dose
595 administration should start at the low end of the dosing range, reflecting the greater frequency of
596 decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy (See
597 **CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION**).

598 **In 12-week clinical trials, RYZOLT™ was administered to 534 patients aged 65 years and older.**
599 **Of those, 68 patients were 75 years of age and older. Comparable incidence rates of patients**
600 **experiencing adverse events were observed for patients older than 65 years of age compared with**
601 **younger patients (< 65 years of age), except constipation for which the incidence was higher in**
602 **older patients. RYZOLT™ should be used with caution in patients older than 75 years of age (See**
603 **CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).**

604

605

606 **Adverse Reactions**

607

608 **RYZOLT™ was administered to a total of 2707 subjects (2406 patients and 301 healthy**
609 **volunteers) during clinical studies, including four randomized double-blind studies (treatment ≥**
610 **12 weeks) and two open-label long-term studies (treatment up to 12 months) in patients with**
611 **moderate to severe pain due to osteoarthritis of the knee. A total of 844 patients were exposed to**
612 **RYZOLT™ for 12 weeks, 493 patients for 6 months and 243 patients for 12 months. Treatment**
613 **emergent adverse events increased with dose from 100 mg to 300 mg in the three twelve-week,**
614 **randomized, double-blind, placebo-controlled studies (Table 2).**

615

616 **Table 2. Percentage of Patients with Incidence of Adverse Events ≥ 2% from Three**
617 **12-week Placebo-Controlled Studies (MDT3-002, MDT3-003 and MDT3-**
618 **005).**

ADVERSE EVENTS (MEDRA Preferred Terms)	RYZOLT™			Total*	Placebo N=668
	100 mg N=216	200 mg N=311	300 mg N=530		
Nausea	28 (13%)	42 (14%)	76 (14%)	179 (16%)	37 (6%)
Constipation	21 (10%)	36 (12%)	52 (10%)	140 (13%)	26 (4%)

Dizziness	16 (7%)	28 (9%)	52 (10%)	106 (10%)	18 (3%)
Somnolence	11 (5%)	22 (7%)	23 (4%)	77 (7%)	12 (2%)
Vomiting	7 (3%)	16 (5%)	31 (6%)	58 (5%)	4 (1%)
Pruritus	9 (4%)	15 (5%)	18 (3%)	51 (5%)	7 (1%)
Headache	10 (5%)	9 (3%)	15 (3%)	41 (4%)	21 (3%)
Sweating increased	1 (0%)	9 (3%)	14 (3%)	35 (3%)	5 (1%)
Dry mouth	7 (3%)	13 (4%)	6 (1%)	32 (3%)	8 (1%)
Fatigue	6 (3%)	7 (2%)	9 (2%)	26 (2%)	6 (1%)
Anorexia	4 (2%)	4 (1%)	10 (2%)	25 (2%)	2 (0%)
Vertigo	2 (1%)	3 (1%)	6 (1%)	21 (2%)	3 (0%)
Insomnia	2 (1%)	6 (2%)	9 (2%)	18 (2%)	8 (1%)

619 **Due to the difference in study design of MDT3-005, only the results of the double-blind phase of the study are*
620 *presented and the dose specific results include maintenance period data only.*

621

622 The majority of patients who experienced the most common adverse events ($\geq 5\%$) reported mild
623 to moderate symptoms. Less than 3% of adverse events were rated as severe. Overall, onset of
624 these adverse events usually occurred within the first two weeks of treatment.

625

626 **Adverse reactions with an incidence of 1.0% to <5.0%**

627

628 *Ear and labyrinth disorders:* vertigo

629

630 *Gastrointestinal disorders:* abdominal pain, diarrhea, dry mouth, dyspepsia, upper abdominal
631 pain

632

633 *General disorders:* fatigue, weakness

634

635

636 *Investigations:* weight decreased

637

638 *Metabolism and nutrition disorders:* anorexia

639

640 *Musculoskeletal and connective tissue disorders:* arthralgia

641

642 *Nervous system disorders:* headache, tremor

643

644 *Psychiatric disorders:* anxiety, insomnia

645

646 *Skin and subcutaneous tissue disorders:* pruritus, sweating increased

647

648 *Vascular disorders:* hot flushes

649

650 **Adverse reactions with an incidence of <1.0%**

651

652 *Blood and lymphatic system disorders:* anemia, thrombocytopenia

653

654 *Cardiac disorders:* bradycardia,

655 |
656 |
657 |
658 | *Eye disorders:* blurred vision, visual disturbance
659 |
660 | *Gastrointestinal disorders:* abdominal discomfort, abdominal distension, abdominal tenderness,
661 | change in bowel habit, constipation aggravated, diverticulitis, diverticulum, dyspepsia
662 | aggravated, dysphagia, fecal impaction, (D) (+) gastric irritation, gastritis, gastrointestinal
663 | hemorrhage, gastrointestinal irritation, gastro-esophageal reflux disease, lower abdominal pain,
664 | pancreatitis aggravated, rectal hemorrhage, rectal prolapse, retching
665 |
666 | *General disorders:* asthenia, ±malaise;
667 |
668 | *Hepatobiliary disorders:* biliary tract disorder, cholelithiasis
669 |
670 | *Immune system disorders:* hypersensitivity;
671 |
672 |
673 | *Investigations:* alanine aminotransferase decreased, alanine aminotransferase increased, aspartate
674 | aminotransferase decreased, aspartate aminotransferase increased, blood amylase increased, ±
675 | blood creatinine increased, blood in stool, blood potassium abnormal, blood pressure increased
676 | gamma glutamyltransferase increased;
677 |
678 | *Metabolism and nutrition disorders:* appetite decreased, dehydration;
679 |
680 |
681 | *Nervous system disorders:* ataxia, disturbance in attention, dysarthria, ±gait abnormal, headache
682 | aggravated, mental impairment, ±sedation, seizure, sleep apnea syndrome, syncope, tremor
683 |
684 | *Psychiatric disorders:* abnormal behavior, agitation, anxiety, ±confusion, depression, emotional
685 | disturbance, euphoric mood, indifference, irritability, libido decreased, nervousness, sleep
686 | disorder
687 |
688 | *Renal and urinary disorders:* difficulty in micturition, ±urinary hesitation, ±urinary retention
689 |
690 | *Reproductive system and breast disorders:* erectile dysfunction, sexual dysfunction;
691 |
692 | *Respiratory, thoracic and mediastinal disorders:* dyspnea
693 | ±
694 | *Skin and subcutaneous tissue disorders:* allergic dermatitis, cold sweat, ±dermatitis, night sweats,
695 | pallor, generalized pruritus, urticaria
696 |
697 |
698 | *Vascular disorders:* flushing, hypertension, hypotension, orthostatic hypotension
699 |

700 **Overdosage**

701 |
702 | Acute overdosage with tramadol can be manifested by respiratory depression, somnolence
703 | progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted
704 | pupils, bradycardia, hypotension and death.

705 Death due to overdose have been reported with abuse and misuse of tramadol, by ingesting,
706 inhaling, or injecting the crushed tablets. The risk of fatal overdose is further increased when
707 tramadol is abused concurrently with alcohol and other CNS depressants, including other opioids.

708

709 In the treatment of tramadol overdosage, primary attention should be given to the re-
710 establishment of a patent airway and institution of assisted or controlled ventilation. Supportive
711 measures (including oxygen and vasopressors) should be employed in the management of
712 circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or
713 arrhythmias may require cardiac massage or defibrillation.

714 While naloxone will reverse some (but not all) symptoms caused by overdosage with tramadol,
715 the risk of seizures is also increased with naloxone administration. In animals, convulsions
716 following the administration of toxic doses of tramadol could be suppressed with barbiturates or
717 benzodiazepines but were increased with naloxone. Naloxone administration did not change the
718 lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose
719 because it removes less than 7% of the administered dose in a 4-hour dialysis period.

720

721

Dosage and Administration

722

723 **RYZOLT™** extended-release tablets should be taken once a day. The tablets should be
724 **swallowed whole with liquid and not split, chewed, dissolved or crushed.** **RYZOLT™** tablets
725 produce a continuous release of active ingredient over 24 hours: a repeat dosage within 24 hours
726 is not recommended.

727

Patients Not Currently on Tramadol Immediate-Release Products:

729 **Treatment with RYZOLT™ should be initiated** at a dose of 100 mg/day. Daily doses should be
730 titrated by 100 mg/day increments every 2-3 days (i.e., start 200 mg/day on day 3 or 4 of therapy)
731 to achieve a balance between adequate pain control and tolerability for the individual patient. For
732 patients requiring the 300 mg daily dose, titration should take at least 4 days (i.e. 300 mg/day on
733 day 5). The usual daily dose is 200 or 300 mg. The daily dose and titration should be
734 individualized for each patient. Therapy should be continued with the lowest effective dose.
735 **RYZOLT™** should not be administered at a dose exceeding 300 mg per day.

736 Clinical experience suggests that signs and symptoms of withdrawal may be reduced by tapering
737 medication when discontinuing tramadol therapy.

738

Patients Currently on Tramadol Immediate-Release Products:

740 For patients maintained on tramadol immediate release (IR) products, the 24-hour tramadol IR
741 dose should be calculated and the patient should **be initiated on a total daily dose of RYZOLT™**
742 rounded down to the next lowest 100 mg increment. The dose may subsequently be
743 individualized according to patient need. Due to limitations in flexibility of dose selection with
744 **RYZOLT™, some patients maintained on tramadol** IR products may not be able to convert to
745 **RYZOLT™.** **RYZOLT™** should not be administered at a dose **exceeding 300 mg per day.** Do
746 **not use RYZOLT™ with other tramadol products. (see WARNINGS).**

747

Individualization of Dose

749 Good pain management practice dictates that analgesic dose be individualized according to
750 patient need using the lowest beneficial dose. Studies with tramadol products in adults have

751 shown that starting at the lowest possible dose and titrating upward will result in fewer
752 discontinuations and increased tolerability.

753

754 **Renal and Hepatic Disease**

755 **RYZOLT™** should not be used in patients with:

- 756 • Creatinine clearance less than 30 mL/min,
- 757 • Hepatic impairment.

758 (See **WARNINGS, Use in Renal and Hepatic Disease**).

759

760 **Geriatric patients (65 years of age and older)**

761 In general, dose selection for patients over 65 years of age who may have decreased hepatic or
762 renal function, or other concomitant diseases, should be initiated cautiously, usually starting at the
763 **low end of the dosing range. RYZOLT™** should be administered with greater caution at the
764 lowest effective dose in patients over 75 years, due to the potential for greater frequency of
765 adverse events in this population.

766

767 **How Supplied**

768

769 **RYZOLT™** (tramadol hydrochloride extended-release tablets) are supplied in a number of
770 packages and dose strengths:

771

772 100-mg, white, beveled edge, round biconvex tablets, plain on one side and printed "PP 100" in
773 black ink on the other side.

774 **Bottle of 30 tablets – NDC 59011-334-30**

775 **Bottle of 90 tablets – NDC 59011-334-90**

776 (b) (4)

777 (b) (4)

778

779 200-mg, white, beveled edge, round biconvex tablets, plain on one side and printed "PP 200" in
780 black ink on the other side

781 **Bottle of 30 tablets – NDC 59011-335-30**

782 **Bottle of 90 tablets – NDC 59011-335-90**

783 (b) (4)

784 (b) (4)

785

786 300-mg, white, beveled edge, round biconvex tablets, plain on one side and printed "PP 300" in
787 black ink on the other side

788 **Bottle of 30 tablets – NDC 59011-336-30**

789 **Bottle of 90 tablets – NDC 59011-336-90**

790 (b) (4)

791 (b) (4)

792

793 Store at 25°C (77°F); excursions permitted between 15-30°C (59 – 86°F). Dispense in a tight, light-
794 resistant container.
795
796 Warning: keep out of reach of children.
797 Manufactured by:
798 Confab Laboratories, Inc
799 Saint-Hubert, Quebec, Canada J3Y 3X3
800
801 Distributed by:
802 Purdue Pharma L.P.
803 Stamford, CT 06901-3431
804
805 Licensed from Labopharm Europe Limited
806
807 U.S. Patents 6,607,748; U.S. Patent 5,591,452; U.S. Patent 6,254,887
808 RYZOLT™ is a trademark of Purdue Pharma L.P.
809

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sharon Hertz

12/30/2008 12:56:44 PM

Appears This Way
On Original