

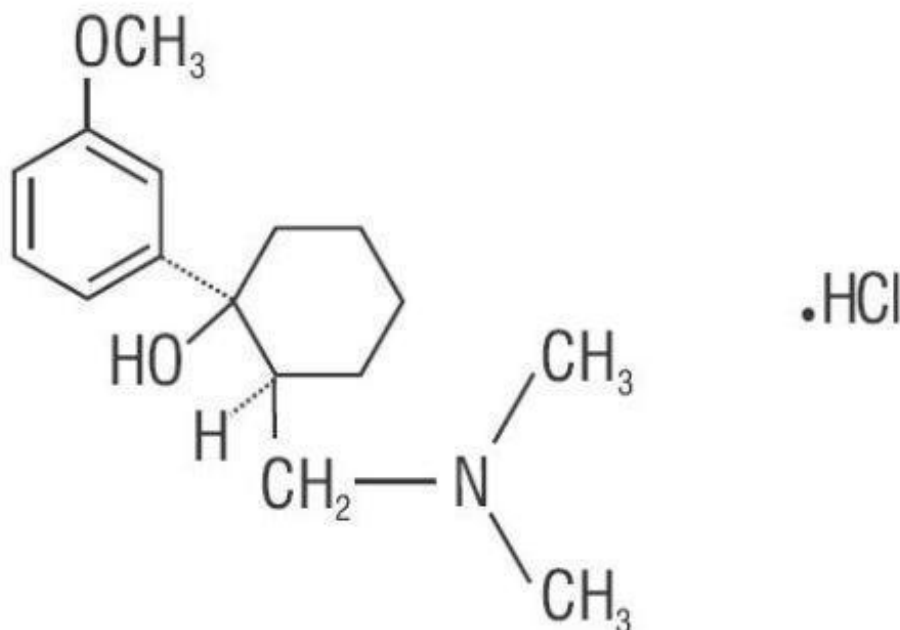
**TRAMADOL HCL ER- tramadol hcl tablet, extended release**  
**TRAMADOL HYDROCHLORIDE- tramadol hydrochloride tablet, extended release**  
**TRAMADOL HYDROCHLORIDE- tramadol hydrochloride tablet, coated**  
**DIRECT RX**

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**TRAMADOL HYDROCHLORIDE**

**DESCRIPTION SECTION**

Tramadol hydrochloride is a centrally acting synthetic analgesic in an extended-release formulation. The chemical name is (±)cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:

Figure 1



The molecular weight of tramadol hydrochloride is 299.84. It is a white, crystalline powder that is freely soluble in water and methanol, very slightly soluble in acetone and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. Tramadol hydrochloride extended-release tablets contain 100 mg, 200 mg or 300 mg of tramadol hydrochloride, USP in an extended-release formulation. The tablets are white in color and contain the inactive ingredients pregelatinized maize starch, hypromellose, mannitol, magnesium stearate, cellulose acetate and polyethylene glycol.

Imprinting ink contains, shellac glaze, iron oxide black, N-butyl alcohol, ammonium hydroxide and propylene glycol.

**CLINICAL PHARMACOLOGY SECTION**

• Mechanism of Action

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to  $\mu$ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to  $\mu$ -opioid receptors. In animal models, M1 is up to 6 times

more potent than tramadol in producing analgesia and 200 times more potent in  $\mu$ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. The relationship between exposure of tramadol and M1 and efficacy has not been evaluated in the tramadol hydrochloride extended-release tablets clinical studies.

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

#### Pharmacokinetics

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. Tramadol hydrochloride is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

The pharmacokinetics of tramadol are approximately dose-proportional over a 100 mg to 400 mg dose range in healthy subjects. The observed tramadol AUC values for the 400 mg dose were 26% higher than predicted based on the AUC values for the 200 mg dose. The clinical significance of this finding has not been studied and is not known.

#### Absorption

In healthy subjects, the bioavailability of a tramadol hydrochloride extended-release 200 mg tablet relative to a 50 mg every six hours dosing regimen of the immediate-release dosage form (tramadol) was approximately 85 to 90%. Consistent with the extended-release nature of the formulation, there is a lag time in drug absorption following tramadol hydrochloride extended-release tablets administration. The mean peak plasma concentrations of tramadol and M1 after administration of tramadol hydrochloride extended-release tablets to healthy volunteers are attained at about 12 h and 15 h, respectively, after dosing (see Table 1 and Figure 2). Following administration of the tramadol hydrochloride extended-release tablets, steady-state plasma concentrations of both tramadol and M1 are achieved within four days with once daily dosing.

The mean (%CV) pharmacokinetic parameter values for tramadol hydrochloride extended-release tablets 200 mg administered once daily and tramadol hydrochloride immediate-release 50 mg administered every six hours are provided in Table 1.

**Table 1. Mean (% CV) Steady-State Pharmacokinetic Parameter Values (n=32).**

Pharmacokinetic Parameter	Tramadol		M1 Metabolite	
	Tramadol Hydrochloride Extended-Release 200 mg Tablet Once-Daily	Immediate-Release Tramadol 50 mg Tablet Every 6 Hours	Tramadol Hydrochloride Extended-Release 200 mg Tablet Once-Daily	Immediate-Release Tramadol 50 mg Tablet Every 6 Hours
AUC <sub>0-24</sub> (ng·h/mL)	5975 (34)	6613 (27)	1890 (25)	2095 (26)
C <sub>max</sub> (ng/mL)	335 (35)	383 (21)	95 (24)	104 (24)
C <sub>min</sub> (ng/mL)	187 (37)	228 (32)	69 (30)	82 (27)
T <sub>max</sub> (h)	12 (27)	1.5 (42)	15 (27)	1.9 (57)
% Fluctuation	61 (57)	59 (35)	34 (72)	26 (47)

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AUC<sub>0-24</sub>: Area Under the Curve in a 24-hour dosing interval; C<sub>max</sub>: Peak Concentration in a 24-hour dosing interval; C<sub>min</sub>: Trough Concentration in a 24-hour dosing interval; T<sub>max</sub>: Time to Peak Concentration

Figure 2: Mean Steady-State Tramadol (a) and M1 (b) Plasma Concentrations on Day 8 Post Dose after Administration of 200 mg Tramadol Hydrochloride Extended-Release Tablet Once-Daily and 50 mg Immediate-Release Tramadol Tablet Every 6 Hours.

a. Tramadol

b. M1

#### Food Effects

After a single dose administration of 200 mg tramadol hydrochloride extended-release tablet with a high fat meal, the C<sub>max</sub> and AUC<sub>0-∞</sub> of tramadol decreased 28% and 16%, respectively, compared to fasting conditions. Mean T<sub>max</sub> was increased by 3 hr (from 14 hr under fasting conditions to 17 hr under fed conditions). While tramadol hydrochloride extended-release tablets may be taken without regard to food, it is recommended that it be taken in a consistent manner.

#### Distribution

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

#### Metabolism

Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N – (mediated by CYP3A4 and CYP2B6) and O – (mediated by CYP2D6) demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyl tramadol, denoted M1) is pharmacologically active in animal models.

Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS - Drug Interactions).

#### Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 after administration of tramadol hydrochloride extended-release tablets are approximately 7.9 and 8.8 hours, respectively.

#### Special Populations

##### Renal

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of tramadol hydrochloride extended-release tablets 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CL<sub>cr</sub>: 50 to 80 mL/min) or moderate (CL<sub>cr</sub>: 30 to 50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20 to 40% with increased severity of the renal impairment (from normal to mild and moderate). Tramadol hydrochloride extended-release tablets have not been studied in patients with severe renal impairment (CL<sub>cr</sub> < 30 mL/min). The limited availability of dose strengths of tramadol hydrochloride extended-release tablet does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe renal impairment (see PRECAUTIONS, Use in Renal and Hepatic Disease and DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

##### Hepatic

Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of tramadol hydrochloride extended-release tablets 100 mg. The exposure of (+)- and (-)-tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)- M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of tramadol hydrochloride extended-release tablets has not been studied in patients with severe hepatic impairment. After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function. The limited availability of dose strengths of tramadol hydrochloride extended-release tablets does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe hepatic impairment (see PRECAUTIONS, Use in Renal and Hepatic Disease and DOSAGE AND ADMINISTRATION).

#### Geriatric

The effect of age on the absorption of tramadol from tramadol hydrochloride extended-release tablets in patients over the age of 65 years has not been studied and is unknown (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

#### Gender

Based on pooled multiple-dose pharmacokinetics studies for tramadol hydrochloride extended-release tablets in 166 healthy subjects (111 males and 55 females), the dose-normalized AUC values for tramadol were somewhat higher in females than in males. There was a considerable degree of overlap in values between male and female groups. Dosage adjustment based on gender is not recommended.

#### Drug Interactions

The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Tramadol is also metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol hydrochloride extended-release tablets may affect the metabolism of tramadol leading to altered tramadol exposure (see PRECAUTIONS, Drug Interactions).

#### Quinidine

Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg quinidine two hours before the administration of tramadol hydrochloride extended-release tablets 100 mg. The results demonstrated that the exposure of tramadol increased 50 to 60% and the exposure of M1 decreased 50 to 60% (see PRECAUTIONS, Drug Interactions). In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

#### Carbamazepine

Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride extended-release tablets and carbamazepine is not recommended (see PRECAUTIONS, Drug Interactions).

## Cimetidine

Concomitant administration of tramadol immediate-release tablets with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the tramadol hydrochloride extended-release tablets dosage regimen with cimetidine is recommended.

## CLINICAL STUDIES SECTION

- Tramadol hydrochloride was studied in patients with chronic, moderate to moderately severe pain due to osteoarthritis and/or low back pain in four 12-week, randomized, double-blind, placebo-controlled trials. To qualify for inclusion into these studies, patients were required to have moderate to moderately severe pain as defined by a pain intensity score of  $\geq 40$  mm, off previous medications, on a 0 mm to 100 mm visual analog scale (VAS). Adequate evidence of efficacy was demonstrated in the following two studies:

In one 12-week randomized, double-blind, placebo-controlled study, patients with moderate to moderately severe pain due to osteoarthritis of the knee and/or hip were administered doses from 100 mg to 400 mg daily. Treatment was initiated at 100 mg QD for four days then increased by 100 mg per day increments every five days to the randomized fixed dose. Between 51% and 59% of patients in the tramadol hydrochloride extended-release tablets treatment groups completed the study and 56% of patients in the placebo group completed the study. Discontinuations due to adverse events were more common in the tramadol hydrochloride extended-release tablets 200 mg, 300 mg and 400 mg treatment groups (20%, 27%, and 30% of discontinuations, respectively) compared to 14% of the patients treated with tramadol hydrochloride extended-release tablets 100 mg and 20% of patients treated with placebo.

Pain, as assessed by the WOMAC Pain subscale, was measured at 1, 2, 3, 6, 9, and 12 weeks and change from baseline assessed. A responder analysis based on the percent change in WOMAC Pain subscale demonstrated a statistically significant improvement in pain for the 100 mg and 200 mg treatment groups compared to placebo (see Figure 3).

In one 12-week randomized, double-blind, placebo-controlled flexible-dosing trial of tramadol hydrochloride extended-release tablets in patients with osteoarthritis of the knee, patients titrated to an average daily tramadol hydrochloride extended-release tablets dose of approximately 270 mg/day. Forty-nine percent of patients randomized to tramadol hydrochloride extended-release tablets completed the study, while 52% of patients randomized to placebo completed the study. Most of the early discontinuations in the tramadol hydrochloride extended-release tablets treatment group were due to adverse events, accounting for 27% of the early discontinuations in contrast to 7% of the discontinuations from the placebo group.

Thirty-four percent of the placebo-treated patients discontinued the study due to lack of efficacy compared to 15% of tramadol hydrochloride extended-release tablets-treated patients. The tramadol hydrochloride extended-release tablets group demonstrated a statistically significant decrease in the mean VAS score, and a statistically significant difference in the responder rate, based on the percent change from baseline in the VAS score, measured at 1, 2, 4, 8, and 12 weeks, between patients receiving tramadol hydrochloride extended-release tablets and placebo (see Figure 4).

Close

## INDICATIONS & USAGE SECTION

Tramadol hydrochloride extended-release tablets are indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time

## CONTRAINDICATIONS SECTION

Tramadol hydrochloride extended-release tablets should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids.

Tramadol hydrochloride extended-release tablets are contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol hydrochloride extended-release tablets may worsen central nervous system and respiratory depression in these patients.

## WARNINGS SECTION

- Seizure Risk

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

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Other opioids.

Administration of tramadol may enhance the seizure risk in patients taking:

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

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

### Suicide Risk

- Do not prescribe tramadol hydrochloride extended-release tablets for patients who are suicidal or addiction-prone.
- Prescribe tramadol hydrochloride extended-release tablets with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.
- Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

### Serotonin Syndrome Risk

The development of a potentially life-threatening serotonin syndrome may occur with use of tramadol products, including tramadol hydrochloride extended-release tablets, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs and triptans, with drugs which impair metabolism of serotonin (including MAOIs) and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur within the recommended dose. (See CLINICAL PHARMACOLOGY - Pharmacokinetics).

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

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

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

#### Anaphylactoid Reactions

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

#### Respiratory Depression

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

#### Interaction With Central Nervous System (CNS) Depressants

Tramadol hydrochloride extended-release tablets should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol hydrochloride extended-release tablets increase the risk of CNS and respiratory depression in these patients.

#### Increased Intracranial Pressure or Head Trauma

Tramadol hydrochloride extended-release tablets should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol hydrochloride extended-release tablets. (see WARNINGS - Respiratory Depression).

#### Use in Ambulatory Patients

Tramadol hydrochloride extended-release tablets may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

#### Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors

Use tramadol hydrochloride extended-release tablets with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol hydrochloride extended-release tablets with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

#### Withdrawal

Withdrawal symptoms may occur if tramadol hydrochloride extended-release tablet is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be reduced by tapering tramadol hydrochloride extended-release tablets.

#### Misuse, Abuse and Diversion of Opioids

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

Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing tramadol hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Tramadol hydrochloride extended-release tablets could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

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

#### Interactions with Alcohol and Drugs of Abuse

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

### **DRUG ABUSE AND DEPENDENCE SECTION**

- Tramadol hydrochloride extended-release tablet is a mu-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion. Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common. “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. Tramadol hydrochloride extended-release tablets, 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. Tramadol hydrochloride extended-release tablets are 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.

#### Risk of Overdosage

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



## PRECAUTIONS SECTION

### Acute Abdominal Condition

The administration of tramadol hydrochloride extended-release tablets may complicate the clinical assessment of patients with acute abdominal conditions.

### Use in Renal and Hepatic Disease

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. Tramadol hydrochloride extended-release tablets have not been studied in patients with severe renal impairment ( $CL_{cr} < 30$  mL/min). The limited availability of dose strengths and once daily dosing of tramadol hydrochloride extended-release tablets do not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. The pharmacokinetics of tramadol hydrochloride extended-release tablets has not been studied in patients with severe hepatic impairment. The limited availability of dose strengths and once daily dosing of tramadol hydrochloride extended-release tablets do not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

## INFORMATION FOR PATIENTS SECTION

- ◦ Patients should be informed that tramadol hydrochloride extended-release tablets is for oral use only and should be swallowed whole. The tablets should not be chewed, crushed, or split.
- Patients should be informed that tramadol hydrochloride extended-release tablets may cause seizures and/or serotonin syndrome with concomitant use of serotonergic agents (including SRIs, NRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.
- Patients should be informed that tramadol hydrochloride extended-release tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Patients should be informed that tramadol hydrochloride extended-release tablets should not be taken with alcohol containing beverages.
- Patients should be informed that tramadol hydrochloride extended-release tablets should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- Female patients should be instructed to inform the prescriber if they are pregnant, think they might become pregnant, or are trying to become pregnant (see PRECAUTIONS, Labor and Delivery).
- Patients should be educated regarding the single-dose and 24-hour dosing regimen, as exceeding these recommendations can result in respiratory depression, seizures or death.

### Use in Drug and Alcohol Addiction

Tramadol hydrochloride extended-release tablet is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

### Drug Interactions

CYP2D6 and CYP3A4 inhibitors: Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (See CLINICAL PHARMACOLOGY - Pharmacokinetics), such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including

seizures and serotonin syndrome.

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

**Triptans:** Based on the mechanism of action of tramadol and the potential for serotonin syndrome, caution is advised when tramadol hydrochloride extended-release tablets are coadministered with a triptan. If concomitant treatment of tramadol hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS - Serotonin Syndrome).

#### Use With Carbamazepine

Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride extended-release tablets and carbamazepine is not recommended.

#### Use With Quinidine

Coadministration of quinidine with tramadol hydrochloride extended-release tablets resulted in a 50% to 60% increase in tramadol exposure and a 50% to 60% decrease in M1 exposure (see CLINICAL PHARMACOLOGY, Drug Interactions). The clinical consequences of these findings are unknown.

#### Use With Digoxin and Warfarin

Postmarketing surveillance of tramadol has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

#### Potential for Other Drugs to Affect Tramadol

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol hydrochloride extended-release tablets may affect the metabolism of tramadol leading to altered tramadol exposure.

#### Potential for Tramadol to Affect Other Drugs

In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when administered concomitantly at therapeutic doses.

Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic effect of tramadol was observed in p53(+/-)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2-fold maximum daily human dose [MDHD] of 400 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks and in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2-fold MDHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug.

Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using *Salmonella* and *E. coli*, a mouse lymphoma assay (in the absence of metabolic activation), and a bone marrow micronucleus test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male

and female rats (approximately equivalent to MDHD).

#### Pregnancy

##### Teratogenic Effects: Pregnancy Category C

Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2-fold MDHD), 80 mg/kg in rats (2-fold MDHD) or 300 mg/kg in rabbits (approximately 15-fold MDHD).

##### Non-teratogenic Effects

Tramadol caused a reduction in neonatal body weight and survival at an oral dose of 80 mg/kg (approximately 2-fold MDHD) when rats were treated during late gestation throughout lactation period.

There are no adequate and well-controlled studies in pregnant women. Tramadol hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during postmarketing reports with tramadol hydrochloride immediate-release products.

##### Labor and Delivery

Tramadol hydrochloride extended-release tablets should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see DRUG ABUSE AND ADDICTION). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol hydrochloride during labor.

The effect of tramadol hydrochloride extended-release tablets, if any, on the later growth, development, and functional maturation of the child is unknown.

##### Nursing Mothers

Tramadol hydrochloride extended-release tablets are not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single intravenous 100 mg dose of tramadol, the cumulative excretion in breast milk within sixteen hours postdose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

##### Pediatric Use

The safety and efficacy of tramadol hydrochloride extended-release tablets in patients under 18 years of age have not been established. The use of tramadol hydrochloride extended-release tablets in the pediatric population is not recommended.

##### Geriatric Use

Nine-hundred-one elderly (65 years of age or older) subjects were exposed to tramadol hydrochloride extended-release tablets in clinical trials. Of those subjects, 156 were 75 years of age and older. In general, higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia. For this reason, tramadol hydrochloride extended-release tablets should be used with great caution in patients older than 75 years of age (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

## ADVERSE REACTIONS SECTION

- Tramadol hydrochloride extended-release tablets were administered to a total of 3108 patients during studies conducted in the U.S. These included four double-blind studies in patients with osteoarthritis and/or chronic low back pain and one open-label study in patients with chronic non-

malignant pain. A total of 901 patients were 65 years or older. The frequency of adverse events generally increased with doses from 100 mg to 400 mg in the two pooled, twelve-week, randomized, double-blind, placebo-controlled studies in patients with chronic non-malignant pain (see Table 2).

**Table 2: Incidence (%) of patients with adverse event rates  $\geq$  5% from two 12-week placebo-controlled studies in patients with moderate to moderately severe chronic pain by dose (N=1811).**

MedDRA Preferred Term	Tramadol Hydrochloride Extended-Release Tablets		Placebo			
	100 mg (N=403) n (%)	200 mg (N=400) n (%)	300 mg (N=400) n (%)	400 mg (N=202) n (%)	(N=406) n (%)	
Dizziness (not vertigo)		64 (15.9)	81 (20.3)	90 (22.5)	57 (28.2)	28 (6.9)
Nausea		61 (15.1)	90 (22.5)	102 (25.5)	53 (26.2)	32 (7.9)
Constipation		49 (12.2)	68 (17)	85 (21.3)	60 (29.7)	17 (4.2)
Headache		49 (12.2)	62 (15.5)	46 (11.5)	32 (15.8)	43 (10.6)
Somnolence		33 (8.2)	45 (11.3)	29 (7.3)	41 (20.3)	7 (1.7)
Flushing		31 (7.7)	40 (10)	35 (8.8)	32 (15.8)	18 (4.4)
Pruritus		25 (6.2)	34 (8.5)	30 (7.5)	24 (11.9)	4 (1)
Vomiting		20 (5)	29 (7.3)	34 (8.5)	19 (9.4)	11 (2.7)
Insomnia		26 (6.5)	32 (8)	36 (9)	22 (10.9)	13 (3.2)
Dry Mouth		20 (5)	29 (7.3)	39 (9.8)	18 (8.9)	6 (1.5)
Diarrhea		15 (3.7)	27 (6.8)	37 (8.5)	10 (5)	17 (4.2)
Asthenia		14 (3.5)	24 (6)	26 (6.5)	13 (6.4)	7 (1.7)
Postural hypotension		7 (1.7)	17 (4.3)	8 (2)	11 (5.4)	9 (2.2)
Sweating increased		6 (1.5)	8 (2)	15 (3.8)	13 (6.4)	1 (0.2)
Anorexia		3 (0.7)	7 (1.8)	21 (5.3)	12 (5.9)	1 (0.2)

The following adverse events were reported from all the chronic pain studies (N=3108).

The lists below include adverse events not otherwise noted in Table 2.

Adverse events with incidence rates of 1% to <5%

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal pain upper, dyspepsia, abdominal pain, sore throat

General disorders: weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain

Infections and infestations: nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis  
Investigations: blood creatine phosphokinase increased, weight decreased  
Metabolism and nutrition disorders: appetite decreased  
Musculoskeletal, connective tissue and bone disorders: arthralgia, back pain, pain in limb, neck pain  
Nervous system disorders: tremor, paresthesia, hypoesthesia  
Psychiatric disorders: nervousness, anxiety, depression, restlessness  
Respiratory, thoracic and mediastinal disorders: sneezing, cough, rhinorrhea, nasal congestion, dyspnea, sinus congestion  
Skin and subcutaneous tissue disorders: sweating increased, dermatitis  
Vascular disorders: hot flushes, vasodilatation  
Adverse events with incidence rates of 0.5% to <1% and serious adverse events reported in at least 2 patients.  
Cardiac disorders: palpitations, myocardial infarction  
Ear and labyrinth disorders: tinnitus, vertigo  
Gastrointestinal disorders: flatulence, toothache, constipation aggravated, appendicitis, pancreatitis  
General disorders: feeling jittery, edema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling  
Hepato-biliary disorders: cholelithiasis, cholecystitis  
Infections and infestations: cellulitis, ear infection, gastroenteritis, pneumonia, viral infection  
Injury and poisoning: joint sprain, muscle injury  
Investigations: alanine aminotransferase increased, blood pressure increased, aspartate aminotransferase increased, heart rate increased, blood glucose increased, liver function tests abnormal  
Musculoskeletal, connective tissue and bone disorders: muscle cramps, muscle spasms, joint stiffness, muscle twitching, myalgia, osteoarthritis aggravated  
Nervous system disorders: migraine, sedation, syncope, disturbance in attention, dizziness aggravated  
Psychiatric disorders: euphoric mood, irritability, libido decreased, sleep disorder, agitation, disorientation, abnormal dreams  
Renal and urinary disorders: difficulty in micturition, urinary frequency, hematuria, dysuria, urinary retention  
Respiratory, thoracic and mediastinal disorders: yawning  
Skin and subcutaneous tissue disorders: contusion, piloerection, clamminess, night sweats, urticaria  
Vascular disorders: hypertension aggravated, hypertension, peripheral ischemia

## **OVERDOSAGE SECTION**

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

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

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

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

## **DOSAGE & ADMINISTRATION SECTION**

Tramadol hydrochloride extended-release tablets should not be used in patients with:  
creatinine clearance less than 30 mL/min,  
severe hepatic impairment (Child-Pugh Class C)

(See PRECAUTIONS, Use in Renal and Hepatic Disease).

Tramadol hydrochloride extended-release tablets must be swallowed whole and must not be chewed, crushed, or split (see WARNINGS, Misuse, Abuse and Diversion of Opioids and DRUG ABUSE AND ADDICTION).

Adults (18 years of age and over)

Patients Not Currently on Tramadol Immediate-Release Products

For patients not currently treated with tramadol immediate-release (IR) products, tramadol hydrochloride extended-release tablets should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100 mg increments every five days to relief of pain and depending upon tolerability. Tramadol hydrochloride extended-release tablets should not be administered at a dose exceeding 300 mg per day.

Patients Currently on Tramadol Immediate-Release Products

For patients maintained on tramadol IR products, calculate the 24-hour tramadol immediate-release (IR) dose and initiate a total daily dose of tramadol hydrochloride extended-release tablets rounded down to the next lowest 100 mg increment. The dose may subsequently be individualized according to patient need. Due to limitations in flexibility of dose selection with tramadol hydrochloride extended-release tablets, some patients maintained on tramadol IR products may not be able to convert to tramadol hydrochloride extended-release tablets. Tramadol hydrochloride extended-release tablets should not be administered at a dose exceeding 300 mg per day. The concomitant use of tramadol hydrochloride extended-release tablets with other tramadol products is not recommended (see WARNINGS).

Individualization of Dose

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Start at the lowest possible dose and titrate upward as tolerated to achieve an adequate effect. Clinical studies of tramadol hydrochloride extended-release tablets have not demonstrated a clinical benefit at a total daily dose exceeding 300 mg.

In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. Tramadol hydrochloride extended-release tablets should be administered with even greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

## **HOW SUPPLIED SECTION**

Tramadol hydrochloride extended-release tablets are supplied in the following package and dose strength forms:

100 mg: White, round shape, biconvex, beveled edge, coated tablet with release portal on the center of

the tablet on any one side, imprinted “531” with black ink on one side and plain on other side.

Bottles of 30's with Child Resistant Cap ..... NDC 47335-859-83

Bottles of 100's with Child Resistant Cap ..... NDC 47335-859-88

Bottles of 100's with Non Child Resistant Cap ..... NDC 47335-859-08

Bottles of 1000's with Non Child Resistant Cap ..... NDC 47335-859-18

200 mg: White, round shape, biconvex, beveled edge, coated tablet with release portal on the center of the tablet on any one side, imprinted “533” with black ink on one side and plain on other side.

Bottles of 30's with Child Resistant Cap ..... NDC 47335-860-83

Bottles of 100's with Child Resistant Cap ..... NDC 47335-860-88

Bottles of 100's with Non Child Resistant Cap ..... NDC 47335-860-08

Bottles of 1000's with Non Child Resistant Cap ..... NDC 47335-860-18

300 mg: White, round shape, biconvex, beveled edge, coated tablet with release portal on the center of the tablet on any one side, imprinted “537” with black ink on one side and plain on other side.

Bottles of 30's with Child Resistant Cap ..... NDC 47335-861-83

Bottles of 100's with Child Resistant Cap ..... NDC 47335-861-88

Bottles of 100's with Non Child Resistant Cap ..... NDC 47335-861-08

Bottles of 1000's with Non Child Resistant Cap ..... NDC 47335-861-18

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in a tight, light resistant container.

Warning: keep out of reach of children.

**WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

### Addiction, Abuse, and Misuse

Tramadol hydrochloride extended-release tablet exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tramadol hydrochloride extended-release tablets, and monitor all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions (5.1)].

### Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see Warnings and Precautions (5.2)]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

### Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of tramadol hydrochloride extended-release tablets. Monitor for respiratory depression, especially during initiation of tramadol hydrochloride extended-release tablets or following a dose increase. Instruct patients to swallow tramadol hydrochloride extended-release tablets intact, and not to cut, break, chew, crush, or dissolve the tablets to avoid exposure to a potentially fatal dose of tramadol [see Warnings and Precautions (5.3)].

### Accidental Ingestion

Accidental ingestion of even one dose of tramadol hydrochloride extended-release tablets, especially by children, can result in a fatal overdose of tramadol [see Warnings and Precautions (5.3)].

### Ultra-Rapid Metabolism Of Tramadol And Other Risk Factors For Life-Threatening Respiratory Depression In Children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism [see Warnings and Precautions (5.4)]. Tramadol hydrochloride extended-release tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. Avoid the use of tramadol hydrochloride extended-release tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects



of tramadol. [see Warnings and Precautions (5.4)]

#### Neonatal Opioid Withdrawal Syndrome

Prolonged use of tramadol hydrochloride extended-release tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.5)].

#### Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol hydrochloride extended-release tablet requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1 [see Warnings and Precautions (5.6), Drug Interactions (7)].

**Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants** Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.7), Drug Interactions (7)].

Reserve concomitant prescribing of tramadol hydrochloride extended-release Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

Extended-release tablets are available as:

100 mg tablets: White to off-white circular, biconvex, beveled edge coated tablets imprinted with 'L010' on one side and plain on the other side.

200 mg tablets: White to off-white circular, biconvex, beveled edge coated tablets imprinted with 'L011' on one side and plain on the other side.

300 mg tablets: White to off-white circular, biconvex, beveled edge coated tablets imprinted with 'L012' on one side and plain on the other side.

Table 2 includes clinically significant drug interactions with tramadol hydrochloride extended-release tablets.

#### Inhibitors of CYP2D6

##### Clinical Impact:

The concomitant use of tramadol hydrochloride extended-release tablets and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of tramadol hydrochloride extended-release tablets is achieved. Since M1 is a more potent  $\mu$ -opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome.

After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression [see Clinical Pharmacology (12.3)].

#### Intervention:

If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures, and serotonin syndrome.

If a CYP2D6 inhibitor is discontinued, consider lowering tramadol hydrochloride extended-release tablets dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.

#### Examples

Quinidine, fluoxetine, paroxetine and bupropion

#### Inhibitors of CYP3A4

#### Clinical Impact:

The concomitant use of tramadol hydrochloride extended-release tablets and CYP3A4 inhibitors can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of tramadol hydrochloride extended-release tablets is achieved.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease [see Clinical Pharmacology (12.3)], resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.

#### Intervention:

If concomitant use is necessary, consider dosage reduction of tramadol hydrochloride extended-release tablets until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals.

If a CYP3A4 inhibitor is discontinued, consider increasing the tramadol hydrochloride extended-release tablets dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.

#### Examples

Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)

#### CYP3A4 Inducers

#### Clinical Impact:

The concomitant use of tramadol hydrochloride extended-release tablets and CYP3A4 inducers can decrease the plasma concentration of tramadol [see Clinical Pharmacology (12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol, [see Warnings and Precautions (5.6)].

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase [see Clinical Pharmacology (12.3)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause seizures and serotonin syndrome, and potentially fatal respiratory depression.

#### Intervention:

If concomitant use is necessary, consider increasing the tramadol hydrochloride extended-release tablets dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal.

If a CYP3A4 inducer is discontinued, consider tramadol hydrochloride extended-release tablets dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression.

Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride extended-release tablets and carbamazepine is not recommended.

#### Examples:

Rifampin, carbamazepine, phenytoin

Benzodiazepines and Other Central Nervous System (CNS) Depressants

#### Clinical Impact:

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

#### Intervention:

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Warnings and Precautions (5.7)] .

#### Examples:

Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

#### Serotonergic Drugs

##### Clinical Impact:

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

##### Intervention:

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue tramadol hydrochloride extended-release tablets if serotonin syndrome is suspected.

##### Examples:

Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

#### Monoamine Oxidase Inhibitors (MAOIs)

##### Clinical Impact:

MAOI interactions with opioids may manifest as serotonin syndrome [see Warnings and Precautions (5.7)] or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.3)] .

##### Intervention:

Do not use tramadol hydrochloride extended-release tablets in patients taking MAOIs or within 14 days of stopping such treatment.

##### Examples:

phenelzine, tranylcypromine, linezolid

#### Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

##### Clinical Impact:

May reduce the analgesic effect of tramadol hydrochloride extended-release tablets and/or precipitate withdrawal symptoms.

##### Intervention:

Avoid concomitant use.

##### Examples:

butorphanol, nalbuphine, pentazocine, buprenorphine

#### Muscle Relaxants

##### Clinical Impact:

Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

##### Intervention:

Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of tramadol hydrochloride extended-release tablets and/or the muscle relaxant as necessary.

#### Diuretics

##### Clinical Impact:

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

#### Intervention:

Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

#### Anticholinergic Drugs

##### Clinical Impact:

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

#### Intervention:

Monitor patients for signs of urinary retention or reduced gastric motility when tramadol hydrochloride extended-release tablets are used concomitantly with anticholinergic drugs.

#### Digoxin

##### Clinical Impact:

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

#### Intervention:

Follow patients for signs of digoxin toxicity and adjust the dosage of digoxin as needed.

#### Warfarin

##### Clinical Impact:

Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.

#### Intervention:

Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

## 8.1 Pregnancy

### Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.5)]. Available data with tramadol hydrochloride extended-release tablets in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

### Clinical Considerations

#### Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.5)].

Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol during post-approval use of tramadol immediate-release products.

## Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Tramadol hydrochloride extended-release tablets are not recommended for use in pregnant women during or immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including tramadol hydrochloride extended-release tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of tramadol hydrochloride extended-release tablets, if any, on the later growth, development, and functional maturation of the child is unknown.

## Data

### Animal Data

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m<sup>2</sup> basis are 1.9, 0.8, and 4.9 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification, and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat, and rabbit are 2.3, 2.6, and 19 times the MRHD, respectively.

Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (1.6 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (2.6 times the MRHD).

## 8.2 Lactation

### Risk Summary

Tramadol hydrochloride extended-release tablets are not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, O-desmethyl tramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding [see Clinical Pharmacology (12.1)]. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with tramadol hydrochloride extended-release tablets.

## Clinical Considerations

If infants are exposed to tramadol hydrochloride through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

### Data

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

## 8.3 Females and Males of Reproductive Potential

### Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)].

## 8.4 Pediatric Use

The safety and effectiveness of tramadol hydrochloride extended-release tablets in pediatric patients have not been established.

Life-threatening respiratory depression and death have occurred in children who received tramadol [see Warnings and Precautions (5.4)]. In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

Tramadol hydrochloride extended-release tablets are contraindicated for all children younger than 12 years of age [see Contraindications (4)].

Tramadol hydrochloride extended-release tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)].

Avoid the use of tramadol hydrochloride extended-release tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. [see Warnings and Precautions (5.4)].

## 8.5 Geriatric Use

Nine-hundred-one elderly (65 years of age or older) subjects were exposed to tramadol hydrochloride extended-release tablets in clinical trials. Of those subjects, 156 were 75 years of age and older. In general, higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia. For this reason, tramadol hydrochloride extended-release tablets should be used with caution in patients over 65 years of age, and with even greater caution in patients older than 75 years of age [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of tramadol hydrochloride extended-release tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.12)].

Tramadol is known to be substantially excreted by the kidney, and the risk of adverse reactions to this

drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

## 8.6 Hepatic Impairment

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. Tramadol hydrochloride extended-release tablet has not been studied in patients with severe hepatic impairment. The limited availability of dose strengths and once daily dosing of tramadol hydrochloride extended-release tablets do not permit the dosing flexibility required for safe use in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe hepatic impairment [see Clinical Pharmacology (12.3)].

## 8.7 Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. Tramadol hydrochloride extended-release tablet has not been studied in patients with severe renal impairment ( $CL_{Cr} < 30$  mL/min). The limited availability of dose strengths and once daily dosing of tramadol hydrochloride extended-release tablets do not permit the dosing flexibility required for safe use in patients with severe renal impairment (Child-Pugh Class C). Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe renal impairment [see Clinical Pharmacology (12.3)].

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### Carcinogenesis

Carcinogenicity assessment has been conducted in mice, rats and p53(+/-) heterozygous mice. A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.5 times the maximum recommended daily human dosage or MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans.

No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water (1 times the MRHD). In a second rat study, no evidence of carcinogenicity was noted in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2-fold the maximum recommended human daily dose MRHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug. No carcinogenic effect of tramadol was observed in p53(+/-)-heterozygous mice at oral doses up to 150 mg/kg/day for 26 weeks.

### Mutagenesis

Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the in vitro bacterial reverse mutation assay using *Salmonella* and *E. coli* (Ames), the mouse lymphoma assay in the absence of metabolic activation, the in vitro chromosomal aberration assay, or the in vivo micronucleus assay in bone marrow.

### Impairment of Fertility

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 1.2 and 1.8 times the maximum recommended human daily dose based on body surface area, respectively.

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Storage and Disposal:

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store tramadol hydrochloride extended-release tablets securely, out of sight and reach of children, and in a

location not accessible by others, including visitors to the home [see Warnings, Drug Abuse and Dependence]. Inform patients that leaving tramadol hydrochloride extended-release tablets unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that medicine take-back options are the preferred way to safely dispose of most types of unneeded medicines. If no take back programs or DEA-registered collectors are available, instruct patients to dispose of tramadol hydrochloride extended-release tablets by following these four steps:

Mix tramadol hydrochloride extended-release tablets (do not crush) with an unpalatable substance such as dirt, cat litter, or used coffee grounds;

Place the mixture in a container such as a sealed plastic bag;

Throw the container in the household trash;

Delete all personal information on the prescription label of the empty bottle

Inform patients that they can visit [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for additional information on disposal of unused medicines.

### Addiction, Abuse, and Misuse

Inform patients that the use of tramadol hydrochloride extended-release tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see Warnings and Precautions (5.1)]. Instruct patients not to share tramadol hydrochloride extended-release tablets with others and to take steps to protect tramadol hydrochloride extended-release tablets from theft or misuse.

### Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting tramadol hydrochloride extended-release tablets or when the dosage is increased, and that it can occur even at recommended dosages [see Warnings and Precautions (5.3)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

### Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see Warnings and Precautions (5.3)]. Instruct patients to take steps to store tramadol hydrochloride extended-release tablets securely and to dispose of unused tramadol hydrochloride extended-release tablets in accordance with the local state guidelines and/or regulations.

### Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise caregivers that tramadol hydrochloride extended-release tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children 12 to 18 years of age receiving tramadol hydrochloride extended-release tablets to monitor for signs of respiratory depression [see Warnings and Precautions (5.4)].

### Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if tramadol hydrochloride extended-release tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see Warnings and Precautions (5.7), Drug Interactions (7)].

### Serotonin Syndrome

Inform patients that tramadol could cause a rare but potentially life-threatening condition, particularly



during concomitant use with serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications [see Warnings and Precautions (5.8), Drug Interactions (7)].

### Seizures

Inform patients that tramadol hydrochloride extended-release tablets may cause seizures with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol [see Warnings and Precautions (5.9)].

### MAOI Interaction

Inform patients not to take tramadol hydrochloride extended-release tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking tramadol hydrochloride extended-release tablets [see Drug Interactions (7)].

### Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see Warnings and Precautions (5.11)].

### Important Administration Instructions

Instruct patients how to properly take tramadol hydrochloride extended-release tablets, including the following:

Tramadol hydrochloride extended-release tablets are designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved tramadol hydrochloride extended-release tablets can result in a fatal overdose [see Dosage and Administration (2.1)].

Advise patients not to exceed the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, hepatic toxicity, and death. [see Dosage and Administration (2.1)].

Do not discontinue tramadol hydrochloride extended-release tablets without first discussing the need for a tapering regimen with the prescriber [see Dosage and Administration (2.4)] .

### Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue tramadol hydrochloride extended-release tablets without first discussing a tapering plan with the prescriber [see Dosage and Administration]

### Hypotension

Inform patients that tramadol hydrochloride extended-release tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see Warnings and Precautions (5.13)].

### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in tramadol hydrochloride extended-release tablets. Advise patients how to recognize such a reaction and when to seek medical attention [see Contraindications (4), Warnings and Precautions (5.16), Adverse Reactions (6)].

### Pregnancy

#### Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of tramadol hydrochloride extended-release tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which

may be life-threatening if not recognized and treated [see Warnings and Precautions (5.5), Use in Specific Populations (8.1)].

#### Embryo-Fetal Toxicity

Inform female patients of reproductive potential that tramadol hydrochloride extended-release tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

#### Lactation

Advise women that breastfeeding is not recommended during treatment with tramadol hydrochloride extended-release tablets [see Use in Specific Populations (8.2)].

#### Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Use in Specific Populations (8.3)].

#### Driving or Operating Heavy Machinery

Inform patients that tramadol hydrochloride extended-release tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see Warnings and Precautions (5.18)].

#### Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see Adverse Reactions (6), Clinical Pharmacology (12.1)].

#### Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

#### Manufactured by:

Lupin Limited

Pithampur (M.P.) - 454 775

INDIA

Revised: May 08, 2019 ID#: 260434

#### Medication Guide

Tramadol Hydrochloride Extended-Release Tablets , CIV

(tram' a dol hye'' droe klor' ide)

Tramadol hydrochloride extended-release tablets are:

A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.

A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Not for use to treat pain that is not around-the-clock.

Important information about tramadol hydrochloride extended-release tablets:

Get emergency help right away if you take too much tramadol hydrochloride extended-release tablets (overdose) . When you first start taking tramadol hydrochloride extended-release tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.

Taking tramadol hydrochloride extended-release tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

Never give anyone else your tramadol hydrochloride extended-release tablets. They could die from taking it. Selling or giving away tramadol hydrochloride extended-release tablets is against the law. Store tramadol hydrochloride extended-release tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

#### Important Information Guiding Use in Pediatric Patients:

Do not give tramadol hydrochloride extended-release tablets to a child younger than 12 years of age. Do not give tramadol hydrochloride extended-release tablets to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.

Avoid giving tramadol hydrochloride extended-release tablets to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not take tramadol hydrochloride extended-release tablets if you have:

severe asthma, trouble breathing, or other lung problems.  
a bowel blockage or have narrowing of the stomach or intestines.

Before taking tramadol hydrochloride extended-release tablets, tell your healthcare provider if you have a history of:

head injury, seizures  
problems urinating  
abuse of street or prescription drugs, alcohol addiction, or mental health problems.  
liver, kidney, thyroid problems  
pancreas or gallbladder problems

Tell your healthcare provider if you are:

pregnant or planning to become pregnant . Prolonged use of tramadol hydrochloride extended-release tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.

breastfeeding . Not recommended-: it may harm your baby.

taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking tramadol hydrochloride extended-release tablets with certain other medicines can cause serious side effects that could lead to death.

When taking tramadol hydrochloride extended-release tablets:

Do not change your dose. Take tramadol hydrochloride extended-release tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.

Take your prescribed dose once a day at the same time every day. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.

Swallow tramadol hydrochloride extended-release tablets whole. Do not cut, break, chew, crush, dissolve, snort, or inject tramadol hydrochloride extended-release tablets because this may cause you to overdose and die.

Call your healthcare provider if the dose you are taking does not control your pain.

Do not stop taking tramadol hydrochloride extended-release tablets without talking to your healthcare provider.

Dispose of expired, unwanted, or unused tramadol hydrochloride extended-release tablets by taking

your drug to an authorized DEA-registered collector or drug take-back program. If one is not available, you can dispose of tramadol hydrochloride extended-release tablets by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash.

While taking tramadol hydrochloride extended-release tablets DO NOT:

Drive or operate heavy machinery, until you know how tramadol hydrochloride extended-release tablet affects you. Tramadol hydrochloride extended-release tablets can make you sleepy, dizzy, or lightheaded.

Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with tramadol hydrochloride extended-release tablets may cause you to overdose and die.

The possible side effects of tramadol hydrochloride extended-release tablets:

constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, seizure. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of tramadol hydrochloride extended-release tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to [dailymed.nlm.nih.gov](http://dailymed.nlm.nih.gov) or [www.lupinpharmaceuticals.com](http://www.lupinpharmaceuticals.com) or call Lupin Pharmaceuticals, Inc. at 1-800-399-2561.

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

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Pithampur (M.P.) - 454 775

INDIA

Revised: May 08, 2019 ID#: 260433

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

Dist By: Sun Pharmaceutical Industries, Inc  
Cranbury, NJ 08512  
NDC 47335-860-83  
Mfg Lot:  
12/10/2015



# TRAMADOL ER C-IV 200mg 30 Tabs

Generic For: **ULTRAM ER**  
Each extended-release coated tablet contains  
200mg of tramadol hydrochloride. USP

Lot#  
Prod# 893-30

Discard After: 04/18

Packaged and  
Distributed By: **DIRECT Rx**

Alpharetta,  
GA 30005

AEHLX

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.  
**RX ONLY-KEEP OUT OF REACH OF CHILDREN**  
Dosage: See package insert. Store between 68-77 degrees F

NDC 61919-893-30



May cause dizziness, nausea,  
headache, dry mouth, and diarrhea

TRAMADOL ER C-IV 200mg  
NDC 61919-893-30 30 Tabs  
Lot Exp Date 04/18  
Mfg NDC 47335-860-83

TRAMADOL ER C-IV 200mg  
NDC 61919-893-30 30 Tabs  
Lot Exp Date 04/18  
Mfg NDC 47335-860-83

TRAMADOL ER C-IV 200mg  
NDC 61919-893-30 30 Tabs  
Lot Exp Date 04/18  
Mfg NDC 47335-860-83

TRAMADOL ER C-IV 200mg  
NDC 61919-893-30 30 Tabs  
Lot Exp Date 04/18  
Mfg NDC 47335-860-83

Dist By: Amneal Pharmaceuticals LLC  
Gibsonville, NC 27241  
NDC 65162-627-11  
Mfg Lot:  
5/30/2018



# TRAMADOL HCL C-IV 50mg 21 Tabs

Generic For: **ULTRAM**  
Each tablet contains: Tramadol Hydrochloride, USP  
50mg

Lot#  
Prod# 073-21

Discard After: 09/20

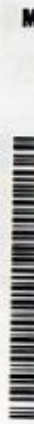
Packaged and  
Distributed By: **DIRECT Rx**

Alpharetta,  
GA 30005

AD00AL

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.  
**RX ONLY-KEEP OUT OF REACH OF CHILDREN**  
Dosage: See package insert. Store between 68-77 degrees F

NDC 61919-073-21



May cause dizziness, nausea,  
headache, dry mouth, and  
diarrhea

TRAMADOL HCL C-IV 50mg  
NDC 61919-073-21 21 Tab  
Lot Exp Date 09/20  
Mfg NDC 65162-627-11

TRAMADOL HCL C-IV 50mg  
NDC 61919-073-21 21 Tab  
Lot Exp Date 09/20  
Mfg NDC 65162-627-11

TRAMADOL HCL C-IV 50mg  
NDC 61919-073-21 21 Tab  
Lot Exp Date 09/20  
Mfg NDC 65162-627-11

TRAMADOL HCL C-IV 50mg  
NDC 61919-073-21 21 Tab  
Lot Exp Date 09/20  
Mfg NDC 65162-627-11

Dist By: Lupin Pharmaceuticals, Inc.  
Baltimore, MD 21202  
NDC 68180-697-06  
Mfg Lot:  
RC 3/25/2019 761340



# TRAMADOL HCL ER C-IV 100mg 60 Tabs

Generic For: **ULTRAM ER**  
each extended-release tablet contains tramadol  
hydrochloride USP 100 mg

Lot# 25MA1915  
Prod# 4332-100-60

Discard After: 9/30/21  
61919-0818-60  
25MA1915  
9/30/21 DAWSONVILLE,  
AT655 GA 30534

Packaged and  
Distributed By: **DIRECT Rx**

AT655

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.  
**RX ONLY-KEEP OUT OF REACH OF CHILDREN**  
Dosage: See package insert. Store between 68-77 degrees F

NDC 61919-0818-60



TRAMADOL HCL ER C-IV 100mg  
NDC 61919-0818-60 60 Tabs  
Lot 25MA1915 Exp Date 09/21  
Mfg NDC 68180-697-06

TRAMADOL HCL ER C-IV 100mg  
NDC 61919-0818-60 60 Tabs  
Lot 25MA1915 Exp Date 09/21  
Mfg NDC 68180-697-06

TRAMADOL HCL ER C-IV 100mg  
NDC 61919-0818-60 60 Tabs  
Lot 25MA1915 Exp Date 09/21  
Mfg NDC 68180-697-06

TRAMADOL HCL ER C-IV 100mg  
NDC 61919-0818-60 60 Tabs  
Lot 25MA1915 Exp Date 09/21  
Mfg NDC 68180-697-06

## TRAMADOL HCL ER

tramadol hcl tablet, extended release

### Product Information

Product Type

HUMAN

Item Code (Source)

NDC:61919-

<b>Product Type</b>	PREScription DRUG	<b>Item Code (Source)</b>	818(NDC:68180-697)
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CIV

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TRAMADOL HYDROCHLORIDE (UNII: 9N7R477WCK) (TRAMADOL - UNII:39J1LGJ30J)	TRAMADOL HYDROCHLORIDE	100 mg

### Inactive Ingredients

Ingredient Name	Strength
DIBUTYL SEBACATE (UNII: 4W5IH7FLNY)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
SHELLAC (UNII: 46N107B71O)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
FERROSO FERRIC OXIDE (UNII: XM0M87F357)	
POVIDONE (UNII: FZ989GH94E)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4U)	

### Product Characteristics

<b>Color</b>	white (white to off-white)	<b>Score</b>	no score
<b>Shape</b>	ROUND (biconvex)	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	L010
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-818-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/03/2019	
2	NDC:61919-818-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/03/2019	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200503	05/03/2019	

## TRAMADOL HYDROCHLORIDE

tramadol hydrochloride tablet, extended release

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:61919-893(NDC:47335-860)
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Route of Administration ORAL

DEA Schedule CIV

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
TRAMADOL HYDROCHLORIDE (UNII: 9N7R477WCK) (TRAMADOL - UNII:39J1LGJ30J)	TRAMADOL HYDROCHLORIDE	200 mg

**Inactive Ingredients**

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MANNITOL (UNII: 3OWL53L36A)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
SHELLAC (UNII: 46N107B71O)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	

**Product Characteristics**

Color	white	Score	no score
Shape	ROUND	Size	11mm
Flavor		Imprint Code	533
Contains			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-893-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/26/2015	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201384	01/01/2014	

**TRAMADOL HYDROCHLORIDE**

tramadol hydrochloride tablet, coated

**Product Information**

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:61919-073(NDC:65162-627)
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Route of Administration ORAL

DEA Schedule

CIV

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
TRAMADOL HYDROCHLORIDE (UNII: 9N7R477WCK) (TRAMADOL - UNII:39J1LGJ30J)	TRAMADOL HYDROCHLORIDE	50 mg

**Inactive Ingredients**

Ingredient Name	Strength
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	

**Product Characteristics**

Color	white	Score	no score
Shape	ROUND	Size	9mm
Flavor		Imprint Code	AN;627
Contains			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-073-21	21 in 1 BOTTLE; Type 0: Not a Combination Product	06/15/2018	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076003	06/15/2018	

**Labeler** - DIRECT RX (079254320)**Establishment**

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-893, 61919-073) , relabel(61919-818)