

TRAMADOL HYDROCHLORIDE - tramadol hydrochloride tablet, extended release
Sun Pharmaceutical Industries, Inc.

Tramadol Hydrochloride Extended-Release Tablets, C-IV
Rx Only

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 tablets expose 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].

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]. 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 [see WARNINGS].

Accidental Ingestion

Accidental ingestion of tramadol hydrochloride extended-release tablets, especially by children, can result in a fatal overdose of tramadol hydrochloride extended-release tablets [see WARNINGS].

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]. 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]. 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].

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].

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 hydrochloride are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Tramadol Extended-Release Tablets requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1 [see WARNINGS, PRECAUTIONS; Drug Interactions].

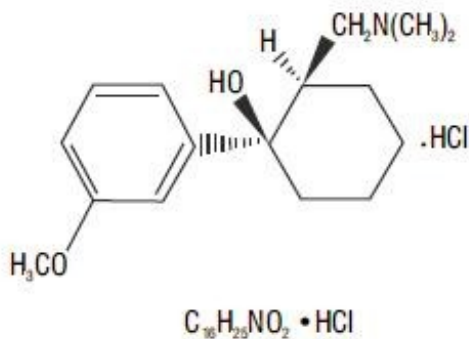
Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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, Precautions; Drug Interactions].

- Reserve concomitant prescribing of tramadol hydrochloride extended-release tablets 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.

DESCRIPTION

Tramadol hydrochloride extended-release tablets are an opioid agonist composed of a matrix delivery system with extended-release characteristics. The chemical name for tramadol hydrochloride, USP is (\pm)cis-2-[(dimethylamino) methyl]-1-(3 methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride, USP is 299.8. Tramadol hydrochloride, USP is a white crystalline powder that is freely soluble in water and ethanol. Tramadol hydrochloride extended-release tablets are for oral administration and contain 100 mg, 200 mg or 300 mg of tramadol hydrochloride, USP. The tablets are white in color. The inactive ingredients in the tablet are pregelatinized maize starch, hypromellose, mannitol, magnesium stearate, cellulose acetate and

polyethylene glycol.

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Tramadol hydrochloride extended-release tablets, contain tramadol, an opioid agonist inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action of tramadol is not completely understood, the analgesic effect of tramadol is believed to be due to binding to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the *O*-demethylated metabolite (M1) to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -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.

Apart from analgesia, tramadol hydrochloride administration may produce various 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.

Pharmacodynamics

Effects on the Central Nervous System

Tramadol produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Tramadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Tramadol causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Tramadol produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see **ADVERSE REACTIONS**]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see **ADVERSE REACTIONS**].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent opioid agonists. The minimum effective analgesic concentration of tramadol for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see **DOSAGE and ADMINISTRATION**].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing tramadol plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see **DOSAGE and ADMINISTRATION**].

Pharmacokinetics

Tramadol hydrochloride extended-release tablets are formulated as a racemate and both tramadol and M1 are detected in the circulation.

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

Absorption

The median time to peak plasma concentrations of tramadol and M1 after multiple-dose administration of a tramadol hydrochloride extended-release tablet 200 mg to healthy subjects are attained at about 4 h and 5 h, respectively (Table 1 and Figure 1).

The pharmacokinetic parameter values of a tramadol hydrochloride extended-release tablet 200 mg administered once daily and tramadol immediate-release 50 mg administered every six hours are provided in Table 1. The relative bioavailability of a 200 mg tramadol hydrochloride extended-release tablet compared to a 50 mg immediate-release tablet dosed every six hours was approximately 95% in healthy subjects.

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

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 ₀₋₂₄ (ng·h/mL)	5991 (22)	6399 (28)	1361 (27)	1438 (23)
C _{max} (ng/mL)	345 (21)	423 (23)	71 (27)	79 (22)
C _{min} (ng/mL)	157 (31)	190 (34)	41 (30)	50 (29)
T _{max} (hr)*	4.0 (3.0 to 9.0)	1.0 (1.0 to 3.0)	5.0 (3.0 to 20)	1.5 (1.0 to 3.0)
Fluctuation (%)	77 (26)	91 (22)	53 (29)	49 (26)

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

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

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

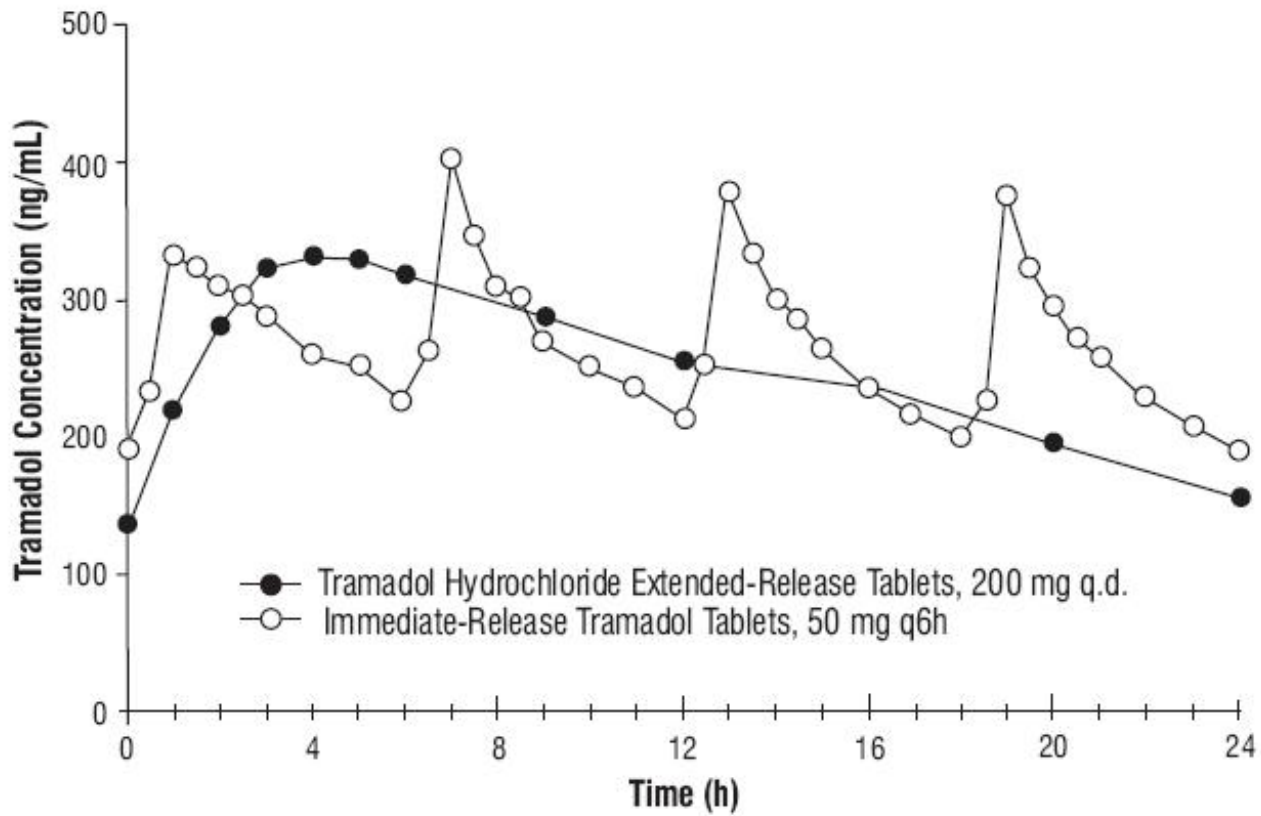
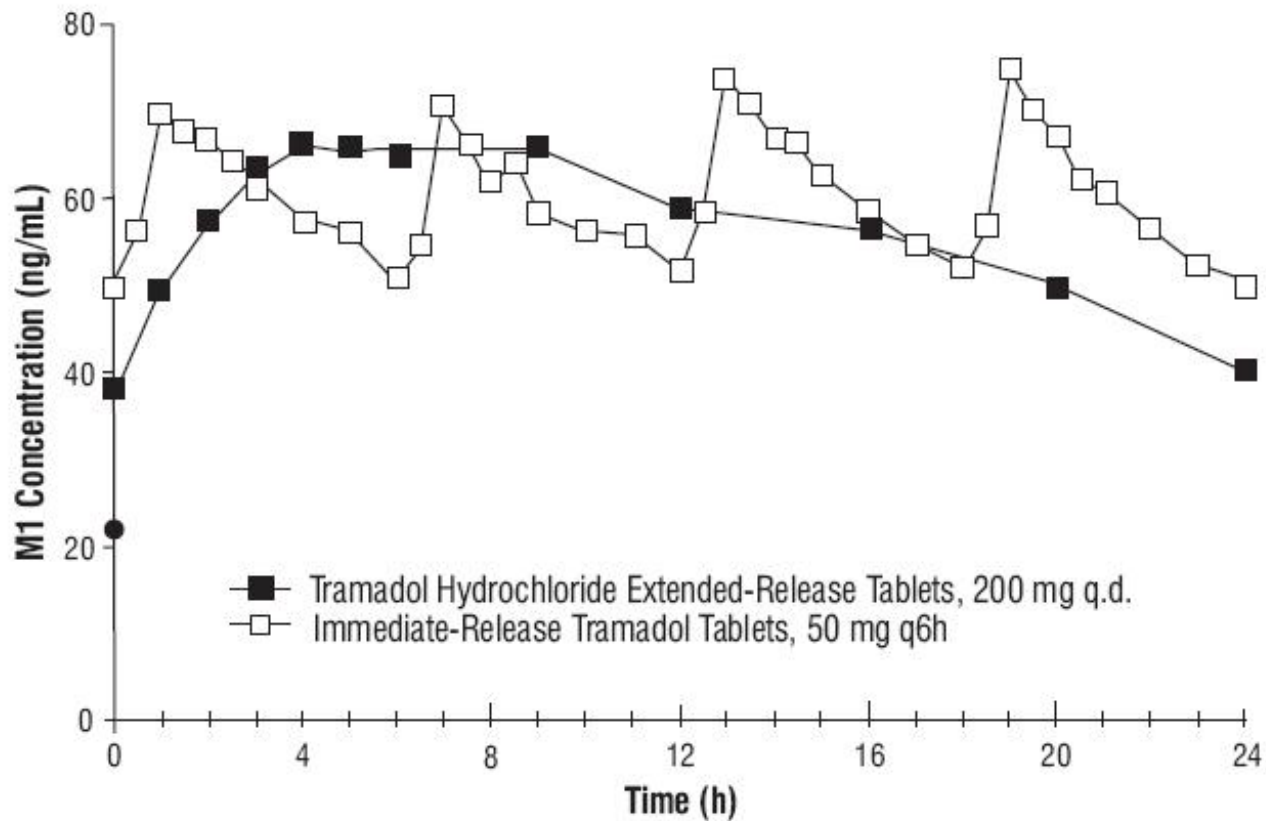


Figure 2. Mean M1 Plasma Concentrations at Steady State Following Five Days of Oral Administration of A Tramadol Hydrochloride Extended-Release Tablet 200 mg Once Daily and Immediate-Release Tramadol 50 mg Every 6 Hours



Food Effect

Coadministration with a high fat meal did not significantly affect AUC (overall exposure to tramadol); however, C_{max} (peak plasma concentration) increased 67% following a single 300 mg tablet administration and 54% following a single 200 mg tablet administration. Tramadol hydrochloride extended-release tablets were administered without regard to food in all clinical trials.

Distribution

The volume of distribution of tramadol is 2.6 and 2.9 L/kg in males and females, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20%. Protein 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.

Elimination

After single administration of tramadol hydrochloride extended-release tablets, the mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.5 ± 1.5 and 7.5 ± 1.4 hours, respectively.

Metabolism

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

Excretion

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.

Special Populations

Hepatic Impairment

The metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve (AUC) for tramadol and longer mean tramadol and M1 elimination half-lives (13 hours for tramadol and 19 hours for M1) after the administration of tramadol immediate-release tablets. Tramadol hydrochloride extended-release tablets have not been studied in patients with 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 hepatic impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with hepatic impairment [see **WARNINGS, Use in Renal and Hepatic Disease and DOSAGE and ADMINISTRATION**].

Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1 in patients taking an immediate-release formulation of tramadol. Tramadol hydrochloride extended-release tablets have not been studied in patients with renal 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 renal impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) [see **WARNINGS, 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.

Geriatric Patients

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

Sex

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

Drug Interaction Studies

Potential for Tramadol to Affect Other Drugs

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data.

Poor/Extensive Metabolizers, CYP2D6

The formation of the active metabolite of tramadol, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of CYP2D6. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. In studies in healthy subjects administered immediate-release tramadol products, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower.

CYP2D6 Inhibitors

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.

Quinidine

Quinidine is a selective inhibitor of CYP2D6, so that concomitant administration of quinidine and tramadol hydrochloride extended-release tablets may result in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown [see **PRECAUTIONS**]. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has

no effect on quinidine metabolism.

CYP3A4 Inhibitors and Inducers

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**].

Cimetidine

Concomitant administration of tramadol immediate-release tablets with cimetidine, a weak CYP3A4 inhibitor, 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.

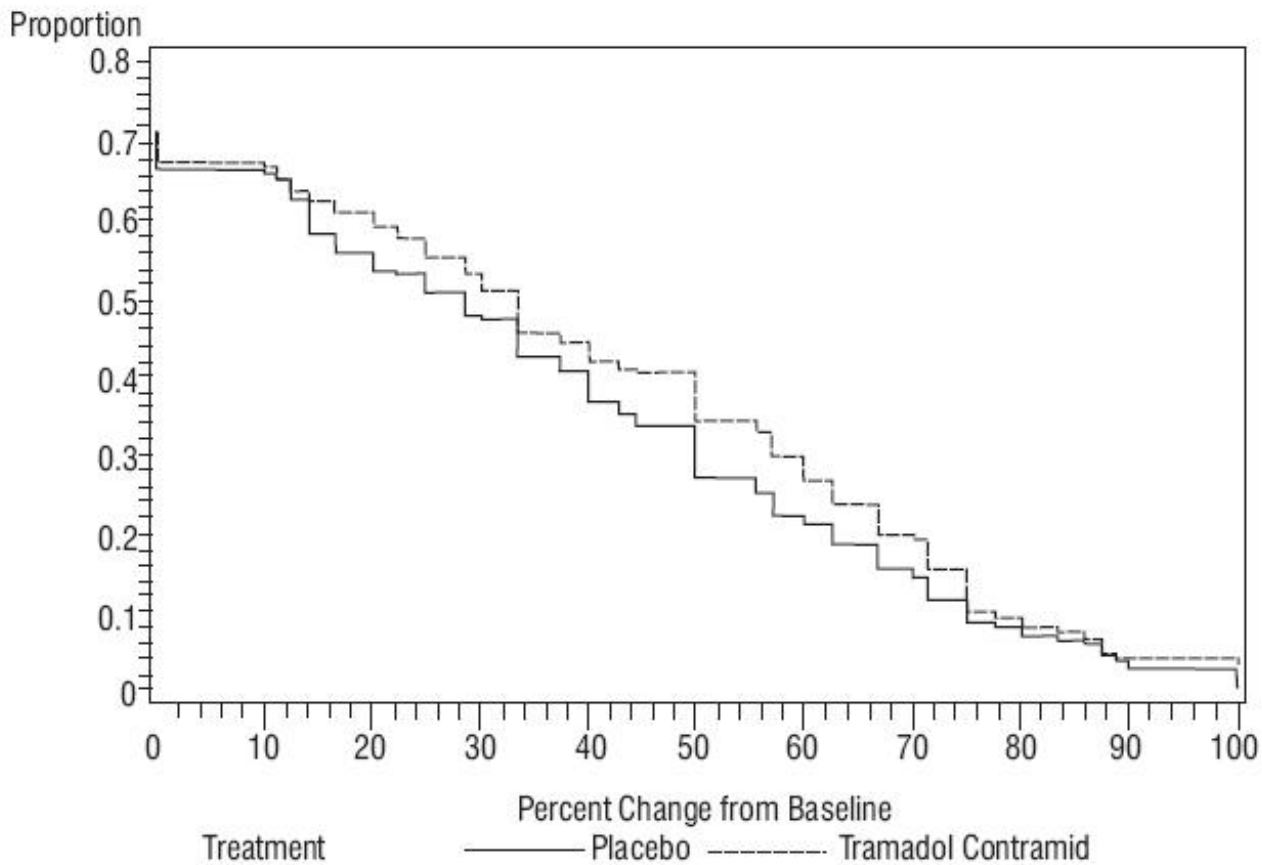
Carbamazepine

Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Concomitant administration of tramadol hydrochloride extended-release tablets and carbamazepine is not recommended [see **PRECAUTIONS**].

CLINICAL STUDIES

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

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



INDICATIONS AND USAGE

Tramadol hydrochloride extended-release tablets are indicated for the management of pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations [see **WARNINGS**], reserve tramadol hydrochloride extended-release tablets or use in patients for whom alternative treatment options [e.g., non-opioid analgesics or immediate-release opioids], are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Tramadol hydrochloride extended-release tablets are not indicated as an as-needed (prn) analgesic.

CONTRAINDICATIONS

Tramadol hydrochloride extended-release tablets are contraindicated for:

- all children younger than 12 years of age [see **WARNINGS**].
- postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see **WARNINGS**].

Tramadol hydrochloride extended-release tablets are also contraindicated in patients with:

- Significant respiratory depression [see **WARNINGS**]

- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see WARNINGS*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see WARNINGS*]
- Hypersensitivity to tramadol (e.g., anaphylaxis) [*see ADVERSE REACTIONS*]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days [*see PRECAUTIONS; Drug Interactions*]

WARNINGS

Addiction, Abuse, and Misuse

Tramadol hydrochloride extended-release tablets contain tramadol, a Schedule IV controlled substance. As an opioid, tramadol hydrochloride extended-release tablets expose users to the risks of addiction, abuse, and misuse [*see DRUG ABUSE and DEPENDENCE*]. Because extended-release products such as tramadol hydrochloride extended-release tablets deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of tramadol present [*see DRUG ABUSE and DEPENDENCE*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed tramadol hydrochloride extended-release tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing tramadol hydrochloride extended-release tablets, and monitor all patients receiving tramadol hydrochloride extended-release tablets for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as tramadol hydrochloride extended-release tablets, but use in such patients necessitates intensive counseling about the risks and proper use of tramadol hydrochloride extended-release tablets along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [*see WARNINGS; Life-Threatening Respiratory Depression, DOSAGE and ADMINISTRATION; Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose*].

Abuse or misuse of tramadol hydrochloride extended-release tablets by cutting, breaking, chewing, crushing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of tramadol and can result in overdose and death [*see OVERDOSAGE*].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing tramadol hydrochloride extended-release tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see PRECAUTIONS; Information for Patients*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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 Risk Evaluation and Mitigation Strategy (REMS) for these products. 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 do all of the following:

- Complete a *REMS-compliant education program* offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The *Patient Counseling Guide (PCG)* can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see **OVERDOSAGE**]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of tramadol hydrochloride extended-release tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of tramadol hydrochloride extended-release tablets.

To reduce the risk of respiratory depression, proper dosing and titration of tramadol hydrochloride extended-release tablets are essential [see **DOSAGE and ADMINISTRATION**]. Overestimating the tramadol hydrochloride extended-release tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of tramadol hydrochloride extended-release tablets, especially by children, can result in respiratory depression and death due to an overdose of tramadol.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see **PRECAUTIONS; Information for Patients**].

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see **DOSAGE and ADMINISTRATION**].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with tramadol hydrochloride extended-release tablets. Inform patients and caregivers about the

various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [*see PRECAUTIONS; Information for Patients*].

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of other CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [*see WARNINGS; Addiction, Abuse, and Misuse, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants, PRECAUTIONS; Information for Patients*].

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. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. 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*].
- 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*].
- 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.
- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose [*see PRECAUTIONS/Pediatric Use, OVERDOSAGE*].

Nursing Mothers

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking tramadol hydrochloride extended-release tablets could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with tramadol hydrochloride extended-release tablets (*see PRECAUTIONS/Nursing Mothers*).

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene

duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see **OVERDOSAGE**]. Therefore, individuals who are ultra-rapid metabolizers should not use tramadol hydrochloride extended-release tablets.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of tramadol hydrochloride extended-release tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see **PRECAUTIONS; Information for Patients, Pregnancy**].

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from tramadol hydrochloride extended-release tablets are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol hydrochloride extended-release tablets require careful consideration of the effects on the parent drug, tramadol which is a weak serotonin and norepinephrine reuptake inhibitor and μ -opioid agonist, and the active metabolite, M1, which is more potent than tramadol in μ -opioid receptor binding [see **PRECAUTIONS; Drug Interactions**].

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of tramadol hydrochloride extended-release tablets with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. A decrease in M1 exposure in patients who have developed physical dependence to tramadol, may result in signs and symptoms of opioid withdrawal and reduced efficacy. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in tramadol plasma levels and an increase in active metabolite M1 levels, which could increase or prolong adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression.

Follow patients receiving tramadol hydrochloride extended-release tablets and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when tramadol hydrochloride extended-release tablets are used in conjunction with inhibitors of CYP2D6 [see **PRECAUTIONS; Drug Interactions**].

Cytochrome P450 3A4 Interaction

The concomitant use of tramadol hydrochloride extended-release tablets with cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g.,

ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in tramadol plasma concentrations, which could increase or prolong adverse reactions, increase the risk for serious adverse events including seizures and serotonin syndrome, and may cause potentially fatal respiratory depression.

The concomitant use of tramadol hydrochloride extended-release tablets with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower tramadol levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Follow patients receiving tramadol hydrochloride extended-release tablets and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when tramadol hydrochloride extended-release tablets are used in conjunction with inhibitors and inducers of CYP3A4 [*see PRECAUTIONS; Drug Interactions*].

Risks of Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of tramadol hydrochloride extended-release tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [*see PRECAUTIONS; Drug Interactions*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [*see WARNINGS; Life-Threatening Respiratory Depression, DOSAGE and ADMINISTRATION; Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose*].

Advise both patients and caregivers about the risks of respiratory depression and sedation when tramadol hydrochloride extended-release tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see PRECAUTIONS; Information for Patients, Drug Interactions*].

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of tramadol hydrochloride extended-release tablets with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see **PRECAUTIONS; Drug Interactions**]. This may occur within the recommended dosage range.

Serotonin syndrome symptoms 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, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue tramadol hydrochloride extended-release tablets if serotonin syndrome is suspected.

Increased Risk of Seizures

Seizures have been reported in patients receiving tramadol hydrochloride within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses above the recommended range.

Concomitant use of tramadol hydrochloride increases the seizure risk in patients taking [see **PRECAUTIONS; Drug Interactions**]:

- Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Other opioids.
- Tramadol hydrochloride extended-release tablets Monoamine Oxidase (MAO) inhibitors [see **WARNINGS; Use with MAO Inhibitors and Serotonin Re-uptake Inhibitors and PRECAUTIONS; Drug Interactions**],
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of seizures 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, certain metabolic disorders, alcohol and drug withdrawal and CNS infections).

In tramadol overdose, naloxone administration may increase the risk of seizures.

Suicide Risk

- Do not prescribe tramadol hydrochloride extended-release tablets for patients who are suicidal or addiction-prone. Consideration should be given to the use of non-narcotic analgesics in patients who are suicidal or depressed [see **DRUG ABUSE and DEPENDENCE**].
- Prescribe tramadol hydrochloride extended-release tablets with caution for patients with history of misuse and/or are currently taking CNS-active drugs including tranquilizers or antidepressant drugs, or alcohol in excess, and patients who suffer from emotional disturbance or depression [see

PRECAUTIONS; Drug Interactions].

Tell your patients not to exceed the recommended dose and to limit their intake of alcohol [see ***DOSAGE and ADMINISTRATION and WARNINGS***].

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one 1 month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Elderly, Cachectic, or Debilitated Patients

The use of tramadol hydrochloride extended-release tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: tramadol hydrochloride extended-release tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of tramadol hydrochloride extended-release tablets [see ***WARNINGS; Respiratory Depression***].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics, including clearance, compared to younger, healthier patients [see ***WARNINGS; Respiratory Depression***].

Monitor such patients closely, particularly when initiating and titrating tramadol hydrochloride extended-release tablets and when tramadol hydrochloride extended-release tablets are given concomitantly with other drugs that depress respiration [see ***WARNINGS; Respiratory Depression***]. Alternatively, consider the use of non-opioid analgesics in these patients.

Severe Hypotension

Tramadol hydrochloride extended-release tablets may cause severe hypotension including hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see ***PRECAUTIONS; Drug Interactions***]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of tramadol hydrochloride extended-release tablets. In patients with circulatory shock tramadol hydrochloride extended-release tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of tramadol hydrochloride extended-release tablets with circulatory

shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), tramadol hydrochloride extended-release tablets may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with tramadol hydrochloride extended-release tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of tramadol hydrochloride extended-release tablets in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

Tramadol hydrochloride extended-release tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The tramadol in tramadol hydrochloride extended-release tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Anaphylaxis and Other Hypersensitivity Reactions

Serious and rarely fatal hypersensitive reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported hypersensitivity reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of hypersensitivity reactions to tramadol and other opioids may be at increased risk and therefore should not receive tramadol hydrochloride extended-release tablets. If anaphylaxis or other hypersensitivity occurs, stop administration of tramadol hydrochloride extended-release tablets immediately, discontinue tramadol hydrochloride extended-release tablets permanently, and do not rechallenge with any formulation of tramadol. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [*see CONTRAINDICATIONS and PRECAUTIONS; Information for Patients*].

Withdrawal

Do not abruptly discontinue tramadol hydrochloride extended-release tablets in a patient physically dependent on opioids. When discontinuing tramadol hydrochloride extended-release tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol hydrochloride extended-release tablets in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [*see DOSAGE and ADMINISTRATION, DRUG ABUSE and DEPENDENCE*].

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including tramadol hydrochloride extended-release tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [*see Drug Interactions*].

Risks of Driving and Operating Machinery

Tramadol hydrochloride extended-release tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of tramadol hydrochloride extended-release tablets and know how they will react to the medication [see **PRECAUTIONS; Information for Patients**].

PRECAUTIONS

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 in patients taking an immediate-release formulation of tramadol. Tramadol hydrochloride extended-release tablets have not been studied in patients with renal 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 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**].

The metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. Tramadol hydrochloride extended-release tablets have not been studied in patients with 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 hepatic impairment. Therefore, tramadol hydrochloride extended-release tablets should not be used in patients with hepatic impairment [see **CLINICAL PHARMACOLOGY and DOSAGE and ADMINISTRATION**].

Information for Patients

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 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**]. 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.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see **WARNINGS, Life Threatening Respiratory Depression**].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with tramadol hydrochloride extended-release tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) [see **WARNINGS, Life Threatening Respiratory Depression; DOSAGE and ADMINISTRATION**].

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered [see **OVERDOSAGE**].

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see **WARNINGS**].

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 all 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 ages 12 to 18 years of age receiving tramadol hydrochloride extended-release tablets to monitor for signs of respiratory depression [see **WARNINGS**].

Interactions with Benzodiazepines or 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; Drug Interactions**].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of 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**].

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**].

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 **PRECAUTIONS; Drug Interactions**].

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**].

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**].
- 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**].
- Do not discontinue tramadol hydrochloride extended-release tablets without first discussing the need for a tapering regimen with the prescriber [see **DOSAGE and ADMINISTRATION**].

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***].

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, ADVERSE REACTIONS***].

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, PRECAUTIONS; Pregnancy***].

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 **PRECAUTIONS; Pregnancy***].

Lactation

Advise women that breastfeeding is not recommended during treatment with tramadol hydrochloride extended-release tablets [*see **PRECAUTIONS; Nursing Mothers***].

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***].

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***].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [*see **ADVERSE REACTIONS, CLINICAL PHARMACOLOGY***].

Drug Interactions

Inhibitors of CYP2D6

The concomitant use of tramadol hydrochloride extended-release tablets and CYP2D6 inhibitors such as quinidine, fluoxetine, paroxetine and bupropion 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 μ -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**].

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.

Inhibitors of CYP3A4

The concomitant use of tramadol hydrochloride extended-release tablets and CYP3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir) 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**], resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.

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.

Inducers of CYP3A4

The concomitant use of tramadol hydrochloride extended-release tablets and CYP3A4 inducers such as rifampin, carbamazepine, phenytoin can decrease the plasma concentration of tramadol, [see **CLINICAL PHARMACOLOGY**], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol [see **WARNINGS**].

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase [see **CLINICAL PHARMACOLOGY**], which could increase or prolong

both the therapeutic effects and adverse reactions, and may cause seizures and serotonin syndrome, and potentially fatal respiratory depression.

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.

Benzodiazepines and other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of respiratory depression, profound sedation, coma, and death.

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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see **WARNINGS**].

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ 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) has resulted in serotonin syndrome.

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.

Monoamine Oxidase Inhibitors (MAOIs)

MAOI interactions with opioids may manifest as serotonin syndrome [see **WARNINGS**] or opioid toxicity (e.g., respiratory depression, coma) [see **WARNINGS**].

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

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist and partial agonist opioid analgesics such as butorphanol, nalbuphine, pentazocine, buprenorphine, may reduce the analgesic effect of tramadol hydrochloride extended-release tablets and/or precipitate withdrawal symptoms. Advise patient to avoid concomitant use of these drugs.

Muscle Relaxants

Tramadol hydrochloride extended-release tablets may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

If concomitant use is warranted, 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. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose [see **WARNINGS**].

Diuretics

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

If concomitant use is warranted, follow patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs

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

If concomitant use is warranted, follow patients for signs and symptoms of urinary retention or reduced gastric motility when tramadol hydrochloride extended-release tablets are used concomitantly with anticholinergic drugs.

Digoxin

Postmarketing surveillance has revealed rare reports of digoxin toxicity. Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.

Warfarin

Postmarketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times. Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

Carcinogenesis, Mutagenesis and 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.

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.

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**].

Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see **WARNINGS**]. 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**].

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

tablets.

Labor and 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/m² 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).

Nursing Mothers

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]. 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

Monitor infants exposed to tramadol hydrochloride extended-release tablets through breast milk 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.

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**]. 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 or high morphine concentrations). 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**].
- 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**].
- 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.

Geriatric Use

In 12-week clinical trials, tramadol hydrochloride extended-release tablets were administered to 534 patients aged 65 years and older. Of those, 68 patients were 75 years of age and older. Comparable incidence rates of patients experiencing adverse events were observed for patients older than 65 years of age compared with younger patients (< 65 years of age), except constipation for which the incidence was higher in older patients. Tramadol hydrochloride extended-release tablets should be used with caution in patients older than 75 years of age [see **CLINICAL PHARMACOLOGY, DOSAGE and ADMINISTRATION**].

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 coadministered 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**].

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.

ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse (see **WARNINGS**)
- Life-Threatening Respiratory Depression (see **WARNINGS**)
- Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-Threatening Respiratory Depression in Children (see **WARNINGS**)
- Neonatal Opioid Withdrawal Syndrome (see **WARNINGS**)
- Interactions with Benzodiazepines or Other CNS Depressants (see **WARNINGS**)
- Serotonin Syndrome (see **WARNINGS**)
- Seizures (see **WARNINGS**)
- Suicide (see **WARNINGS**)
- Adrenal Insufficiency (see **WARNINGS**)
- Severe Hypotension (see **WARNINGS**)
- Gastrointestinal Adverse Reactions (see **WARNINGS**)
- Hypersensitivity Reactions (see **WARNINGS**)
- Withdrawal (see **WARNINGS**)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Tramadol hydrochloride extended-release tablets were administered to a total of 2707 subjects (2406 patients and 301 healthy volunteers) during clinical studies, including four randomized double-blind studies (treatment \geq 12 weeks) and two open-label long-term studies (treatment up to 12 months) in patients with moderate to severe pain due to osteoarthritis of the knee. A total of 844 patients were exposed to tramadol hydrochloride extended-release tablets for 12 weeks, 493 patients for 6 months and 243 patients for 12 months. Treatment emergent adverse events increased with dose from 100 mg to 300 mg in the three twelve-week, randomized, double-blind, placebo-controlled studies (Table 2).

Table 2. Percentage of Patients with Incidence of Adverse Events \geq 2% from Three 12-week Placebo-Controlled Studies (MDT3-002, MDT3-003 and MDT3-005)

ADVERSE EVENTS	Tramadol Hydrochloride Extended-Release Tablets	Placebo
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(MEDRA Preferred Terms)	100 mg N=216	200 mg N=311	300 mg N=530	Total* N=1095	N=668
Nausea	28 (13%)	42 (14%)	76 (14%)	179 (16%)	37 (6%)
Constipation	21 (10%)	36 (12%)	52 (10%)	140 (13%)	26 (4%)
Dizziness	16 (7%)	28 (9%)	52 (10%)	106 (10%)	18 (3%)
Somnolence	11 (5%)	22 (7%)	23 (4%)	77 (7%)	12 (2%)
Vomiting	7 (3%)	16 (5%)	31 (6%)	58 (5%)	4 (1%)
Pruritus	9 (4%)	15 (5%)	18 (3%)	51 (5%)	7 (1%)
Headache	10 (5%)	9 (3%)	15 (3%)	41 (4%)	21 (3%)
Sweating increased	1 (0%)	9 (3%)	14 (3%)	35 (3%)	5 (1%)
Dry mouth	7 (3%)	13 (4%)	6 (1%)	32 (3%)	8 (1%)
Fatigue	6 (3%)	7 (2%)	9 (2%)	26 (2%)	6 (1%)
Anorexia	4 (2%)	4 (1%)	10 (2%)	25 (2%)	2 (0%)
Vertigo	2 (1%)	3 (1%)	6 (1%)	21 (2%)	3 (0%)
Insomnia	2 (1%)	6 (2%)	9 (2%)	18 (2%)	8 (1%)

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

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

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

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: abdominal pain, diarrhea, dry mouth, dyspepsia, upper abdominal pain

General disorders: fatigue, weakness

Investigations: weight decreased

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: arthralgia

Nervous system disorders: headache, tremor

Psychiatric disorders: anxiety, insomnia

Skin and subcutaneous tissue disorders: pruritus, sweating increased

Vascular disorders: hot flushes

Adverse reactions with an incidence of <1.0%

Blood and lymphatic system disorders: anemia, thrombocytopenia

Cardiac disorders: bradycardia

Eye disorders: blurred vision, visual disturbance

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal tenderness, change in bowel habit, constipation aggravated, diverticulitis, diverticulum, dyspepsia aggravated, dysphagia, fecal impaction, gastric irritation, gastritis, gastrointestinal hemorrhage, gastrointestinal irritation, gastro-esophageal reflux disease, lower abdominal pain, pancreatitis aggravated, rectal hemorrhage, rectal prolapse, retching

General disorders: asthenia, malaise

Hepatobiliary disorders: biliary tract disorder, cholelithiasis

Immune system disorders: hypersensitivity

Investigations: alanine aminotransferase decreased, alanine aminotransferase increased, aspartate aminotransferase decreased, aspartate aminotransferase increased, blood amylase increased, blood creatinine increased, blood in stool, blood potassium abnormal, blood pressure increased gamma glutamyltransferase increased

Metabolism and nutrition disorders: appetite decreased, dehydration

Nervous system disorders: ataxia, disturbance in attention, dysarthria, gait abnormal, headache aggravated, mental impairment, sedation, seizure, sleep apnea syndrome, syncope, tremor

Psychiatric disorders: abnormal behavior, agitation, anxiety, confusion, depression, emotional disturbance, euphoric mood, indifference, irritability, libido decreased, nervousness, sleep disorder

Renal and urinary disorders: difficulty in micturition, urinary hesitation, urinary retention

Reproductive system and breast disorders: erectile dysfunction, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: allergic dermatitis, cold sweat, dermatitis, night sweats, pallor, generalized pruritus, urticaria

Vascular disorders: flushing, hypertension, hypotension, orthostatic hypotension

Postmarketing Experience

The following adverse reactions have been identified during post approval use of tramadol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Serotonin syndrome:** Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
- **Adrenal insufficiency:** Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- **Anaphylaxis:** Anaphylaxis has been reported with ingredients contained in tramadol hydrochloride extended-release tablets.
- **Androgen deficiency:** Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Tramadol hydrochloride extended-release tablets contain tramadol, a Schedule IV controlled substance.

Abuse

Tramadol hydrochloride extended-release tablets contain tramadol, a substance with a high potential for abuse similar to other opioids. Tramadol hydrochloride extended-release tablets can be abused and is

subject to misuse, addiction, and criminal diversion [see **WARNINGS**].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful, or potentially harmful, consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. 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 health care providers. “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers 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.

Tramadol hydrochloride extended-release tablets, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, 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.

Risks Specific to Abuse of Tramadol Hydrochloride Extended-Release Tablets

Tramadol hydrochloride extended-release tablets are for oral use only. The abuse of tramadol hydrochloride extended-release tablets poses a risk of overdose and death. The risk is increased with concurrent use of tramadol hydrochloride extended-release tablets with alcohol and other central nervous system depressants. With intravenous abuse the inactive ingredients in tramadol hydrochloride extended-release tablets can result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of

disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue tramadol hydrochloride extended-release tablets in a patient physically dependent on opioids. Rapid tapering of tramadol hydrochloride extended-release tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing tramadol hydrochloride extended-release tablets, gradually taper the dosage using a patient specific plan that considers the following: the dose of tramadol hydrochloride extended-release tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [*see DOSAGE and ADMINISTRATION, WARNINGS*].

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see PRECAUTIONS; Pregnancy*].

OVERDOSAGE

Clinical Presentation

Acute overdose with tramadol hydrochloride extended-release tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see CLINICAL PHARMACOLOGY*].

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to tramadol overdose, administer an opioid antagonist.

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 hydrochloride extended-release tablets 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.

Because the duration of opioid reversal is expected to be less than the duration of action of tramadol in tramadol hydrochloride extended-release tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. Tramadol hydrochloride extended-release tablets will continue to release tramadol and add to the tramadol load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

Tramadol hydrochloride extended-release tablets should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

- Do not use tramadol hydrochloride extended-release tablets concomitantly with other tramadol products [see **WARNINGS**].
- Do not administer tramadol hydrochloride extended-release tablets at a dose exceeding 300 mg per day.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see **WARNINGS**].
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see **WARNINGS**].
- Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with tramadol hydrochloride extended-release tablets and adjust the dosage accordingly [see **WARNINGS**].
- Instruct patients to swallow tramadol hydrochloride extended-release tablets whole [see **PRECAUTIONS; Information for Patients**], and to take it with liquid. Crushing, chewing, splitting, or dissolving tramadol hydrochloride extended-release tablets will result in uncontrolled delivery of tramadol and can lead to overdose or death [see **WARNINGS**].
- Tramadol hydrochloride extended-release tablets may be taken without regard to food, it is recommended that it be taken in a consistent manner [see **CLINICAL PHARMACOLOGY**].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with tramadol hydrochloride extended-release tablets [see **WARNINGS, Life-Threatening Respiratory Depression; PRECAUTIONS, Information for Patients**].

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state

naloxone dispensing and prescribing regulations (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [*see WARNINGS, Addiction, Abuse, and Misuse, Life-Threatening Respiratory Depression, Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants*].

Consider prescribing naloxone when the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

Initial Dosage

Patients Not Currently on a Tramadol Product

The initial dose of tramadol hydrochloride extended-release tablets is 100 mg once daily.

Patients Currently on Tramadol IR Products

Calculate the 24-hour tramadol IR dose and initiate a total daily dose of tramadol hydrochloride extended-release tablets rounded down to the next lower 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.

Conversion from Other Opioids to tramadol hydrochloride extended-release tablets

Discontinue all other around-the-clock opioid drugs when tramadol hydrochloride extended-release tablets therapy is initiated. There are no established conversion ratios for conversion from other opioids to tramadol hydrochloride extended-release tablets defined by clinical trials. Initiate dosing using tramadol hydrochloride extended-release tablets 100 mg once a day.

Titration and Maintenance of Therapy

Individually titrate tramadol hydrochloride extended-release tablets by 100 mg every five days to a dose that provides adequate analgesia and minimizes adverse reactions. The maximum daily dose of tramadol hydrochloride extended-release tablets is 300 mg per day.

Continually reevaluate patients receiving tramadol hydrochloride extended-release tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [*see WARNINGS*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of tramadol hydrochloride extended-release tablets, or may need rescue medication with an appropriate dose of an immediate-release analgesic.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the tramadol hydrochloride extended-release tablets dosage.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Safe Reduction or Discontinuation of Tramadol Hydrochloride Extended-Release Tablets

Do not abruptly discontinue tramadol hydrochloride extended-release tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking tramadol hydrochloride extended-release tablets, there are a variety of factors that should be considered, including the dose of tramadol hydrochloride extended-release tablets the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on tramadol hydrochloride extended-release tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [see **WARNINGS/ Withdrawal, DRUG ABUSE and DEPENDENCE**].

HOW SUPPLIED

Tramadol hydrochloride extended-release tablets are available as follows:

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 47335-531-83

Bottles of 100’s with Child Resistant Cap.....NDC 47335-531-88

Bottles of 100’s with Non Child Resistant Cap.....NDC 47335-531-08

Bottles of 1000’s with Non Child Resistant Cap.....NDC 47335-531-18

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 47335-533-83

Bottles of 100’s with Child Resistant Cap.....NDC 47335-533-88

Bottles of 100’s with Non Child Resistant Cap.....NDC 47335-533-08

Bottles of 1000’s with Non Child Resistant Cap.....NDC 47335-533-18

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 47335-537-83

Bottles of 100’s with Child Resistant Cap.....NDC 47335-537-88

Bottles of 100’s with Non Child Resistant Cap.....NDC 47335-537-08

Bottles of 1000’s with Non Child Resistant Cap.....NDC 47335-537-18

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.

Store tramadol hydrochloride extended-release tablets securely and dispose of properly [see **PRECAUTIONS/ Information for Patients**].

Medication Guide

Tramadol Hydrochloride (tram a dol hye droe klor ide)

Extended-Release Tablets, C-IV

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 or call 911 right away if you take too many 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 many (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- 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 them. 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
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose or mental health 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.
- living in a household where there are small children or someone who has abused street or prescription drugs
- 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 tablets affect 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 or call 911 right away 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 or call 1-800-818-4555**

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

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Sun Pharmaceutical Industries Limited

Halol-Baroda Highway,

Halol-389 350, Gujarat, India.

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PJPI0263J

PRINCIPAL DISPLAY PANEL - Label 100 mg

NDC 47335-531-83

(Once Daily)

Tramadol Hydrochloride Extended-release Tablets CIV

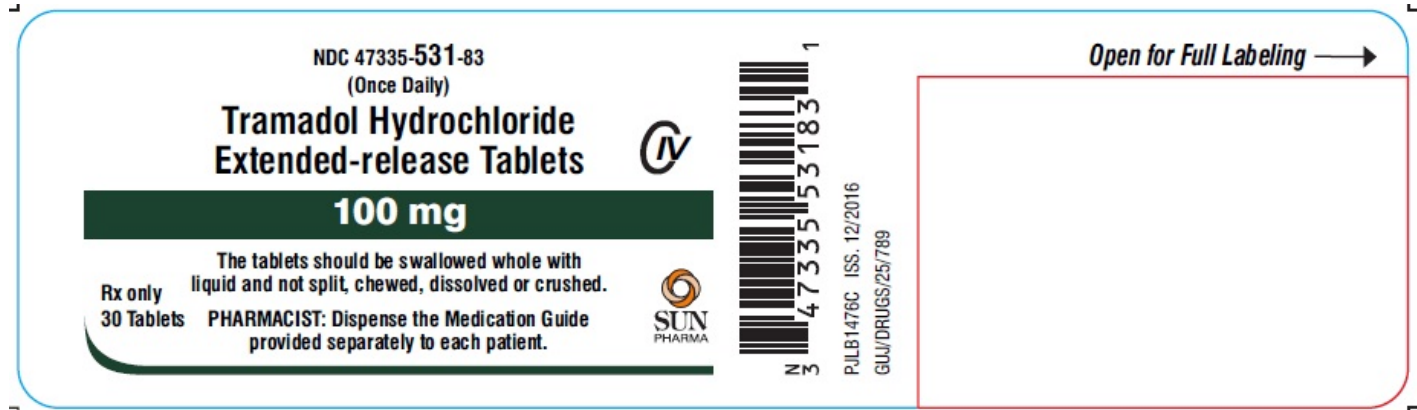
100 mg

The tablets should be swallowed whole with liquid and not split, chewed, dissolved or crushed.

Rx only

30 Tablets

SUN PHARMA



PRINCIPAL DISPLAY PANEL - Label 200 mg

NDC 47335-533-83

(Once Daily)

Tramadol Hydrochloride Extended-release Tablets CIV

200 mg

The tablets should be swallowed whole with liquid and not split, chewed, dissolved or crushed.

Rx only

30 Tablets

SUN PHARMA

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
STARCH, CORN (UNII: O8232NY3SJ)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
MANNITOL (UNII: 3OWL53L36A)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
SHELLAC (UNII: 46N107B71O)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSO FERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	8mm
Flavor		Imprint Code	531
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:47335-531-83	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
2	NDC:47335-531-88	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
3	NDC:47335-531-08	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
4	NDC:47335-531-18	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091607	12/30/2011	

TRAMADOL HYDROCHLORIDE

tramadol hydrochloride tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:47335-533
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)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
MANNITOL (UNII: 3OWL53L36A)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
SHELLAC (UNII: 46N107B71O)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
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:47335-533-83	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
2	NDC:47335-533-88	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
3	NDC:47335-533-08	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
4	NDC:47335-533-18	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091607	12/30/2011	

TRAMADOL HYDROCHLORIDE

tramadol hydrochloride tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:47335-537
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	300 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
MANNITOL (UNII: 3OWL53L36A)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
SHELLAC (UNII: 46N107B71O)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	13mm
Flavor		Imprint Code	537
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:47335-537-83	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
2	NDC:47335-537-88	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
3	NDC:47335-537-08	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	
4	NDC:47335-537-18	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/30/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091607	12/30/2011	

Labeler - Sun Pharmaceutical Industries, Inc. (146974886)

Establishment

Name	Address	ID/FEI	Business Operations
Sun Pharmaceutical Industries Limited		725959238	ANALYSIS(47335-531, 47335-533, 47335-537) , MANUFACTURE(47335-531, 47335-533, 47335-537)

Revised: 8/2020

Sun Pharmaceutical Industries, Inc.