594.00 mm

TRAMADOL HYDROCHLORIDE - tramadol hydrochloride tablet, coated
Rubicon Research Private Limited.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRAMADOL HYDROCHLORIDE TABLETS, safely and effectively. See full prescribing information for TRAMADOL HYDROCHLORIDE TABLETS.

TRAMADOL HYDROCHLORIDE tablets, for oral use, C-IV
Initial U.S. Approval — 1995

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF TRAMADOL HYDROCHLORIDE TABLETS
See full prescribing information for complete boxed warning.

- **Tramadol hydrochloride tablets exposes users to the risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tramadol hydrochloride tablets, and monitor regularly for these behaviors or conditions. (5.1)**
- **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. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase. (5.3)**
- **Accidental ingestion of tramadol hydrochloride tablets, especially by children, can result in a fatal overdose of tramadol. (5.3)**
- **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 (5.4).**
- **Tramadol hydrochloride 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 (4). Avoid the use of tramadol hydrochloride 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. (5.4)**
- **Prolonged use of tramadol hydrochloride tablets, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.5)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol hydrochloride tablets requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1. (5.6, 7)**
- **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. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.7, 7)**

——————RECENT MAJOR CHANGES——————

Boxed Warning 09/2020
Indications and Usage (1) 09/2020
Dosage and Administration (2.1, 2.3, 2.4) 09/2020
Warnings and Precautions (5.6) 09/2020

——————INDICATIONS AND USAGE——————

Tramadol hydrochloride is an opioid agonist indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use: (1)

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, reserve tramadol hydrochloride tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

Tramadol hydrochloride tablets should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

——————DOSAGE AND ADMINISTRATION——————

- Tramadol hydrochloride tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of tramadol hydrochloride tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with Tramadol hydrochloride tablets. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.3)
- 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. (2.1).
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with tramadol hydrochloride tablets. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.3, 5.7).
- Start at 25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, tramadol hydrochloride tablets 50 to100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day (2.3, 2.4).
- Severe Renal Impairment: Tramadol hydrochloride tablets dosing interval to 12 hours, and limit maximum daily dose to 200 mg (2.3).
- Severe hepatic impairment: Recommended dose is 50 mg every 12 hours.
- Do not abruptly discontinue tramadol hydrochloride tablets in a physically-dependent patient because rapid discontinuation opioid analgesic has resulted in serious withdrawals symptoms, uncontrolled pain, and suicide. (2.8)

——————DOSAGE FORMS AND STRENGTHS——————

Tablets: 25 mg, 50 mg, 75 mg and 100 mg (3).

——————CONTRAINDICATIONS——————

- Children younger than 12 years of age (4).
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4).
- Significant respiratory depression (4).
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4).
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4).
- Hypersensitivity to tramadol, any other component of this product or opioids (4).
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4).

——————WARNINGS AND PRECAUTIONS——————

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid). (5.8)

Serotonin Syndrome: May be life-threatening. Can occur with use of tramadol alone, with concomitant use of serotonergic drugs, with drugs that impair metabolism of serotonin or tramadol (5.9).

Risk of Seizure: Can occur at the recommended dose of tramadol. Concomitant use with other drugs may increase seizure risk. Risk may increase in patients with epilepsy, a history of seizures, and in patients with a recognized risk for seizures (5.10).

Risk of Suicide: Do not prescribe for suicidal or addiction-prone patients (5.10).

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid (5.11).

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate closely, particularly during initiation and for the first 72 hours. (5.12)

Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of tramadol hydrochloride tablets in patients with impaired volume or blood pressure. (5.13)

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Regularly evaluate for sedation and respiratory depression. Avoid use of tramadol hydrochloride tablets in patients with impaired consciousness or coma (5.14).

——————ADVERSE REACTIONS——————

The most common incidence of treatment-emergent adverse events (≥ 15.0%) in patients from clinical trials were dizziness/vertigo, nausea, constipation, headache, somnolence, vomiting and sweating (6).

To report SUSPECTED ADVERSE REACTIONS, contact Advagen Pharma Ltd. at 866-488-0312 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

——————DRUG INTERACTIONS——————

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with tramadol hydrochloride tablet because they may reduce analgesic effect of tramadol hydrochloride tablets or precipitate withdrawal symptoms (7).

——————USE IN SPECIFIC POPULATIONS——————

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Breastfeeding not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF TRAMADOL HYDROCHLORIDE TABLETS

Addiction, Abuse AND Misuse
Because the use of tramadol hydrochloride tablets exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of tramadol hydrochloride tablets, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Tramadol hydrochloride tablets are essential *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion
Accidental ingestion of even one dose of tramadol hydrochloride tablets, especially by children, can result in a fatal overdose of tramadol *[see Warnings and Precautions (5.2)]*.

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. Reserve concomitant prescribing of tramadol hydrochloride tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome
If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
Healthcare providers are strongly encouraged to complete a REMS compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.5)]*.

Ultra-Rapid Metabolism of Tramadol and other Risk Factors for Life-Threatening Respiratory Depression in Children
Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism *[see Warnings and Precautions (5.6)]*. Tramadol hydrochloride tablets is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*. Avoid the use of tramadol hydrochloride tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol *[see Warnings and Precautions (5.6)]*.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol hydrochloride tablets requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1 *[see Warnings and Precautions (5.7); Drug Interactions (7)]*.

1. INDICATIONS AND USAGE

Tramadol Hydrochloride Tablets, USP are indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration *[see Warnings and Precautions (5.1)]*, reserve tramadol hydrochloride tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

Tramadol hydrochloride tablets should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Do not use Tramadol hydrochloride tablets concomitantly with other tramadol-containing products.
- Tramadol hydrochloride tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)]. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of tramadol hydrochloride tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with tramadol hydrochloride tablets. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.3, 5.7).
- Start at 25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, tramadol hydrochloride tablets 50 to100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day (2.3, 2.4).
- Severe Renal Impairment: Use tramadol hydrochloride tablets dosing interval to 12 hours, and limit maximum daily dose to 200 mg (2.3).
- Severe hepatic impairment: Recommended dose is 50 mg every 12 hours.
- Do not abruptly discontinue tramadol hydrochloride tablets in a physically-dependent patient because rapid discontinuation opioid analgesic has resulted in serious withdrawals symptoms, uncontrolled pain, and suicide. (2.8)

——————DOSAGE FORMS AND STRENGTHS——————

Tablets: 25 mg, 50 mg, 75 mg and 100 mg (3).

——————CONTRAINDICATIONS——————

- Children younger than 12 years of age (4).
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4).
- Significant respiratory depression (4).
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4).
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4).
- Hypersensitivity to tramadol, any other component of this product or opioids (4).
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIS within the last 14 days (4).

——————WARNINGS AND PRECAUTIONS——————

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid). (5.8)

Serotonin Syndrome: May be life-threatening. Can occur with use of tramadol alone, with concomitant use of serotonergic drugs, with drugs that impair metabolism of serotonin or tramadol (5.9).

Risk of Seizure: Can occur at the recommended dose of tramadol. Concomitant use with other drugs may increase seizure risk. Risk may increase in patients with epilepsy, a history of seizures, and in patients with a recognized risk for seizures (5.10).

Risk of Suicide: Do not prescribe for suicidal or addiction-prone patients (5.10).

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid (5.11).

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate closely, particularly during initiation and for the first 72 hours. (5.12)

Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of tramadol hydrochloride tablets in patients with impaired volume or blood pressure. (5.13)

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Regularly evaluate for sedation and respiratory depression. Avoid use of tramadol hydrochloride tablets in patients with impaired consciousness or coma (5.14).

——————ADVERSE REACTIONS——————

The most common incidence of treatment-emergent adverse events (≥ 15.0%) in patients from clinical trials were dizziness/vertigo, nausea, constipation, headache, somnolence, vomiting and sweating (6).

To report SUSPECTED ADVERSE REACTIONS, contact Advagen Pharma Ltd. at 866-488-0312 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

——————DRUG INTERACTIONS——————

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with tramadol hydrochloride tablet because they may reduce analgesic effect of tramadol hydrochloride tablets or precipitate withdrawal symptoms (7).

——————USE IN SPECIFIC POPULATIONS——————

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Breastfeeding not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2024

2.2 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 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 Patient Counseling Information (17)]*.

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. However, 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 exposure or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone. *[see Warnings and Precautions (5.1, 5.7), Patient Counseling Information (17), Overdosage (10)]*.

2.3 Initial Dosage

Initiating Treatment with Tramadol hydrochloride tablets

Initiate treatment at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of Tramadol hydrochloride tablets.

For patients not requiring rapid onset of analgesic effect, the tolerability of tramadol hydrochloride tablets can be improved by initiating therapy with the following titration regimen: Start tramadol hydrochloride tablets at 25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, tramadol hydrochloride tablets 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not exceed 400 mg/day.

Dosage Modification in Patients with Renal Impairment

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

Dosage Modification in Geriatric Patients

Do not exceed a total dose of 300 mg/day in patients over 75 years old.

2.4 Titration and Maintenance of Therapy

Individually titrate tramadol hydrochloride tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving tramadol hydrochloride tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. 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.

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

2.5 Safe Reduction or Discontinuation of tramadol hydrochloride tablets

Do not abruptly discontinue tramadol hydrochloride 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 tablets, there are a variety of factors that should be considered, including the dose of tramadol hydrochloride 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 prescriber goals and expectations are clear and realistic. Where 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 comorbid 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 tablets, it may be advisable to first convert patients to a longer acting opioid analgesic, (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms and allow for titration in smaller steps 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 a lower dosage strength 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, evaluate 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 at extended periods of time and at 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 substantial portion of the risk for abuse, misuse, and diversion is linked to chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.1)]*. Consider pain rehabilitation as needed.

3 DOSAGE FORMS AND STRENGTHS

Tramadol Hydrochloride Tablets, USP 25 mg are white to off white round shaped film coated tablet with debossed with "A" on one side and "77" other side.

Tramadol Hydrochloride Tablets, USP 50 mg are white to off white, capsule-shaped film coated tablet debossed with "A" on one side and scored on the other side.

Tramadol Hydrochloride Tablets, USP 75 mg are white to off white, capsule-shaped film coated tablet debossed with "77" on one side and scored on the other side.

Tramadol Hydrochloride Tablets, USP 100 mg are white to off white, capsule-shaped film coated tablet debossed with "01" on one side and scored on other side.

Tablets: 25 mg, 50 mg, 75 mg and 100 mg (3).

Tramadol Hydrochloride Tablets, USP are contraindicated for:

- all children younger than 12 years of age *[see Warnings and Precautions (5.4)]*.
- post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.4)]*.

Tramadol Hydrochloride Tablets, USP are also contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.12)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.15)]*.
- Hypersensitivity to tramadol, any other component of this product or opioids *[see Warnings and Precautions (5.16)]*.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Tramadol hydrochloride tablets contains tramadol, a Schedule IV controlled substance. As an opioid, tramadol hydrochloride tablets exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed tramadol hydrochloride 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 tablets, and reassess all patients receiving tramadol hydrochloride tablets for the development of these behaviors and 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 tablets, but use in such patients necessitates intensive counseling about the risks and proper use of tramadol hydrochloride tablets along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Opioids are sought for non-medical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing tramadol hydrochloride tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and the proper disposal of unused drug *[see Patient Counseling Information (17)]*. 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.

5.2 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 (10)]*. 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 tablets, the risk is greatest during the initiation of therapy or following a dosage increase of tramadol hydrochloride tablets.

To reduce the risk of respiratory depression, proper dosing and titration of tramadol hydrochloride tablets are essential *[see Dosage and Administration (2)]*. Overestimating the tramadol hydrochloride 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 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 Patient Counseling Information (17)]*.

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 (2.5)]*.

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 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 Patient Counseling Information (17)]*.

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. However, 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 exposure or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone. *[see Warnings and Precautions (5.1, 5.7), Patient Counseling Information (17), Overdosage (10)]*.

5.3 Risks From Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of tramadol hydrochloride tablets with benzodiazepines and/or other CNS depressants including alcohol (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). Because of these risks, reserve concomitant prescribing of these drugs for 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 depressants with opioid analgesics *[see Drug Interactions (7)]*.

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 for signs and symptoms of respiratory depression and sedation. In patients who are prescribed opioids and benzodiazepines or other CNS depressants, recommend that patients inform their healthcare providers of the concomitant use of benzodiazepines or other CNS depressants, and educate them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Advise patients not to combine tramadol hydrochloride tablets with other products containing tramadol without first consulting their healthcare provider.

Use of tramadol hydrochloride tablets for the treatment of opioid dependence is not recommended. Tramadol hydrochloride tablets is not a suitable substitute for buprenorphine for the treatment of opioid dependence. Tramadol hydrochloride tablets is not a suitable substitute for methadone for the treatment of opioid dependence. Tramadol hydrochloride tablets is not a suitable substitute for opioid agonists, opioid agonist/antagonists, or partial agonists for patients who are opioid-dependent.

Tramadol hydrochloride tablets is not a suitable substitute for non-opioid analgesics in patients

CYP3A4 Inducers

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

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

Intervention: If concomitant use is necessary, consider increasing the tramadol hydrochloride tablets dosage until stable drug effects are achieved. Assess patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider tramadol hydrochloride tablets dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.

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 hydrochloride tablets metabolites of tramadol hydrochloride tablets and carbamazepine, concurrent use is not recommended.

Examples: Rifampin, carbamazepine, phenytoin

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Clinical Impact: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Intervention: Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation) *[see Warnings and Precautions (5.7)]*. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3, 5.7)]*.

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

Serotonergic Drugs

Clinical Impact: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter systems has resulted in serotonin syndrome

Intervention: If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue tramadol hydrochloride tablets immediately if serotonin syndrome is suspected.

Examples: 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 (these intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Monoamine Oxidase Inhibitors (MAOIs)

Clinical Impact: MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.8)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.

Intervention: Do not use tramadol hydrochloride tablets in patients taking MAOIs or within 14 days of stopping such treatment.

Examples: phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Clinical Impact: May reduce the analgesic effect of tramadol hydrochloride tablets and/or precipitate withdrawal symptoms.

Intervention: Avoid concomitant use.

Examples: buprenorphine, nalbuphine, pentazocine, buprenorphine

Muscle Relaxants

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

Intervention: Because respiratory depression that may be greater than otherwise expected decreases the dosage of tramadol hydrochloride 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 Dosage and Administration (2.2), Warnings and Precautions (5.3, 5.7)]*.

Diuretics

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

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

Anticholinergic Drugs

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

Intervention: Evaluate patients for signs of urinary retention or reduced gastric motility when tramadol hydrochloride tablets is used concomitantly with anticholinergic drugs.

Digoxin

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

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

Warfarin

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

Intervention: Frequently reevaluate the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

8 USEIN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome.

Available data with tramadol hydrochloride 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 3.5 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 risks 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 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome can present as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.5)]*.

Neonatal seizures, neonatal withdrawal symptoms, fetal death and still birth have been reported during post-marketing.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiological effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Tramadol hydrochloride tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including tramadol hydrochloride 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 excessive 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 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, (100 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m basis are 1.4, 0.6, and 3.6 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 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 1.7, 1.9 and 14.6 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 1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).

8.2 Lactation

Risk Summary

Tramadol hydrochloride 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-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding *[see Clinical Pharmacology (12)]*. 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 excreted 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 tablets *[see Warnings and Precautions (5.5)]*.

Clinical Considerations

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

Data

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

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

8.4 Pediatric Use

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

Life-threatening respiratory depression and death have occurred in children who received tramadol *[see Warnings and Precautions (5.6)]*. In some of the reported cases, these events followed tonsillectomy and/or adenidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

- Tramadol hydrochloride tablets are contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- Tramadol hydrochloride tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

Avoid the use of tramadol hydrochloride tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to 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.

8.5 Geriatric Use

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

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

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 administered in combination with other agents that depress respiration. Titrate the dosage of tramadol hydrochloride tablets slowly in geriatric patients starting at the low end of the dosing range and frequently reevaluate the patient for signs of central nervous and respiratory depression *[see Warnings and Precautions (5.12)]*.

Tramadol is the active substance 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 regularly evaluate renal function.

8.6 Renal and Hepatic Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction is recommended *[see Dosage and Administration (2.3)]*. Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver. In patients with severe hepatic impairment, dosing reduction is recommended *[see Dosage and Administration (2.3)]*.

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

9 Drug Abuse and Dependence

9.1 Controlled Substance

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

9.2 Abuse

Tramadol hydrochloride tablets contains tramadol, a substance with potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.10)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Tramadol hydrochloride tablets increases risk of overdosage, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Tramadol hydrochloride tablets with alcohol and other central nervous system depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent re-evaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Tramadol hydrochloride tablets abuse include those with a history of prolonged use of products containing tramadol, those with a history of drug or alcohol abuse, or those who are psychiatrically ill. Tramadol hydrochloride tablets in combination with other abused drugs.

"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 healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Presumption with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Tramadol hydrochloride tablets, like other opioids, 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 reevaluation 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 tablets Abuse of Tramadol hydrochloride tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of Tramadol hydrochloride tablets with alcohol and other central nervous system depressants.

Tramadol hydrochloride tablets are approved for oral use only. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/opioid 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 use.

Do not abruptly discontinue tramadol hydrochloride tablets in a patient physically dependent on opioids. Rapid tapering of tramadol hydrochloride 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 tablets, gradually taper the dosage using a patient-specific plan that considers the dose, duration of treatment, the physical dependence 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 an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating a dose reduction *[see Dosage and Administration (2.5) and Warnings and Precautions (5.18)]*.

Signs and symptoms of withdrawal from opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[See Use in Specific Populations (8.1)]*.

10. OVERDOSAGE

Clinical Presentation

Acute overdosage with tramadol hydrochloride 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, QT prolongation, hypotension, partial or complete airway obstruction, atypical sneezing, seizures, and death. Marked myotoxicity rather than miosis may be seen with hypoxic overdose situations.

Deaths due to overdose have been reported with abuse and misuse of tramadol *[see Warnings and Precautions (5.1)]*. Deaths have occurred in adolescents and adults ingesting 1 gram of tramadol. The risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Treatment of Overdose

In case of overdose, priorities are the re-establishment 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 serious arrhythmias will require advanced life support techniques. Because strategies for the management of overdose are continuously evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of an overdose.

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

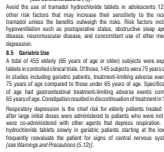
While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol hydrochloride tablets could be suppressed with barbiturates 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 tablets, carefully monitor the patient until spontaneous respiration is adequate. Nevertheless, 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 begun with care and by titration with smaller than usual doses of the antagonist.

11. DESCRIPTION

Tramadol Hydrochloride Tablets, USP for oral use, are an opioid agonist. The chemical name for tramadol hydrochloride is (±-cis-2-[(dimethylamino) methyl]-1-(3- methoxyphenyl) cyclohexanol hydrochloride. The structural formula is:



The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white crystalline powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The octanol/water partition coefficient (log P) is 1.35 at pH 7. Tramadol Hydrochloride Tablets, USP 25 mg, 50 mg, 75 mg and 100 mg contain 25 mg, 50 mg, 75 mg and 100 mg of tramadol hydrochloride, respectively and are white in color. Inactive ingredients in the tablet are hypromellose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polycarbate 80, pregelatinized starch, sodium starch glycolate and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to 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 opioid 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 *[see Clinical Pharmacology (12.2)]*.

Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

12.2 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 administration may produce a constellation of symptoms including nausea and vomiting, dizziness, and somnolence.

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 almost identical findings). Marked myotosis 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.

Effects of intravenous tramadol administration may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

The effect of intravenous tramadol on the QTc*f* interval was evaluated in a double-blind, randomized, four-way crossover, placebo-and positive-(moxifloxacin) controlled study in 68 adult male and female healthy subjects. At a 600 mg dose (1.5-fold the maximum immediate-release daily dose), the study demonstrated no significant effect on the QTc*f* interval.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Warnings and Precautions (5.11), Adverse Reactions (6)]*.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, anorgasmia, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, psychosocial, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on Immune System

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

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with 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 (2)]*.

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 (2)]*.

12.3 Pharmacokinetics

The pharmacokinetic parameters of tramadol hydrochloride tablets is due to both parent drug and the M1 metabolite *[see Clinical Pharmacology (12.2, 12.3)]*. Tramadol is administered as a racemate and both the (+) and (+) forms of both tramadol and M1 are detected in the circulation. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg oral doses.

Absorption

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

Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with four times per day dosing. There is no evidence of self-induction (see Figure 1 and Table 3 below).

Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given four times per day.

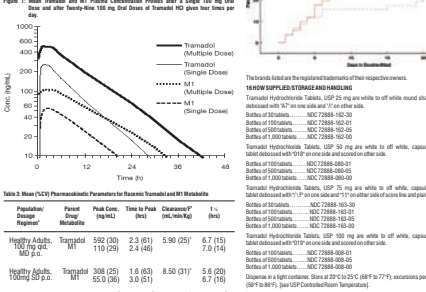


Table 3: Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/ Dosage Regimen*	Parent Drug/ Metabolite	Peak Conc. (ng/mL)	Time to Peak (hrs)	Clearance/F† (mL/min/Kg)	t½ (hrs)
Healthy Adults, 100 mg qid. MD p.o.	Tramadol	592 (30)	2.3 (61)	5.90 (25)‡	6.7 (15)
	M1	110 (29)	2.4 (46)		7.0 (14)
Healthy Adults, 100mg SD p.o.	Tramadol	308 (25)	1.6 (63)	8.50 (31)‡	5.6 (20)
	M1	55.0 (36)	3.0 (51)		6.7 (16)
Geriatric (> 75 yrs) 50 mg SD p.o.	Tramadol	208 (31)‡	2.1 (19)‡	6.89 (25)‡	7.0 (23)‡
	M1				
Hepatic Impaired, 50 mg SD p.o.	Tramadol	217 (11)	1.9 (16)	4.23 (56)‡	13.3 (11)
	M1	19.4 (12)	9.8 (20)		18.5 (15)
Renal Impaired, CLcr<5 mL/ min 100 mg SD i.v.	Tramadol	c	c	4.23 (54)‡	3.73 (17)‡
	M1	c	c		
Renal Impaired, CLcr<5 mL/ min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)‡	11.0 (29)
	M1	c	c		16.9 (18)

*SD = Single dose, MD = Multiple dose, p.o. = Oral administration, i.v. = Intravenous administration, q.i.d. = Four times daily

† F indicates the oral bioavailability of tramadol

‡ Not applicable

c Not measured

Food Effects

Oral administration of tramadol hydrochloride tablets with food does not significantly affect its rate or extent of absorption; therefore, tramadol hydrochloride tablets can be administered without regard to food.

Distribution

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

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean (SD) apparent total clearance of tramadol after a single 100 mg oral dose is 8.50 (31) mL/min/kg. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 (± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing.

Metabolism

Tramadol is extensively metabolized after oral administration by a number of pathways, including O-demethylation, N-demethylation, and conjugation with glucuronic and sulfonic acids. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be N-and O-demethylation and glucuronidation or sulfation in the liver. 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, which may affect the therapeutic response *[Warnings and Precautions (5.4) Drug Interactions (7)]*.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and N-desalkylflurazepam, antidepressive and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of serotonin re-uptake inhibitors and MAO inhibitors may enhance the risk of adverse events, including seizure and serotonin syndrome *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*.

Excretion

Tramadol metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites.

Special Populations

Hepatic Impairment

Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and a longer tramadol and M1 elimination half-life (13 hrs. for tramadol and 19 hrs. for M1). In patients with severe hepatic impairment, adjustment of the dosing regimen is recommended *[see Dosage and Administration (2)]*.

Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction of the dosing regimen is recommended *[see Dosage and Administration (2)]*. The total amount of tramadol removed by a 4-hour hemodialysis session is less than 7% of the administered dose.

Age: Geriatric

Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum plasma concentrations are elevated (208 vs. 192 ng/mL) and the 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 in patients older than 75 years *[see Dosage and Administration (2.3)]*.

Sex

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, 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.

Race / Extensive Metabolizers, CYP2D6

The formation of the active metabolite, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 mediating enzyme system. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in an IMRH mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 300 mg/kg/day of racemic tramadol (0.36 times the MRHD) for approximately two years, although this study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No treatment-related carcinogenicity was noted in a rat 2-year carcinogenicity study looking oral doses of up to 30 mg/kg in the drinking water, 0.73 times the MRHD.

Mutagenesis

Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay, equivocal in the Ames test, and negative 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.

14 CLINICAL STUDIES

Tramadol hydrochloride tablets has been given in single oral dose levels of 50, 75 and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).

In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg tramadol hydrochloride tablets tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.

Tramadol hydrochloride tablets has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol hydrochloride tablets. Patients with a variety of chronic painful conditions were studied in double-blind fashion for up to three months duration. Average daily doses of approximately 250 mg of tramadol hydrochloride tablets in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL with Codeine #3) daily, five doses of aspirin 325 mg with cod