

**TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN- tramadol hydrochloride
and acetaminophen tablet, film coated
Zydus Pharmaceuticals USA Inc.**

HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use TRAMADOL
HYDROCHLORIDE AND ACETAMINOPHEN TABLETS safely and effectively. See full prescribing
information for TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN TABLETS**

TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN TABLETS, for oral use, C-IV

Initial U.S. Approval:2001

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

See full prescribing information for complete boxed warning.

- Tramadol hydrochloride and acetaminophen tablet 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 and acetaminophen tablets, and monitor regularly for these behaviors or conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase. (5.2)
- Accidental ingestion of tramadol hydrochloride and acetaminophen tablets, especially by children, can result in a fatal overdose of tramadol. (5.2)
- 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. (5.3, 7)
- Prolonged use of tramadol hydrochloride and acetaminophen 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. (5.4)
- To ensure that the benefits of opioidanalgesics 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. (5.5)
- 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 (5.6). Tramadol hydrochloride and acetaminophen 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 and acetaminophen 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. (5.6)
- 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 and acetaminophen tablets requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1. (5.7, 7)
- Tramadol hydrochloride and acetaminophen tablets contain acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen containing product. (5.9)

-----**RECENT MAJOR CHANGES**-----

| | |
|---|---------|
| Boxed Warning | 09/2023 |
| Indications and Usage (1) | 04/2023 |
| Dosage and Administration (2.1, 2.3) | 04/2023 |
| Warnings and Precautions; Opioid Induced Hyperalgesia and Allodynia (5.8) | 04/2023 |

-----**INDICATIONS AND USAGE**-----

Tramadol hydrochloride and acetaminophen tablets are a combination of tramadol hydrochloride, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Tramadol hydrochloride and acetaminophen tablets are indicated for short-term use of five days or less. Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or

duration, reserve tramadol hydrochloride and acetaminophen tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- 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 and acetaminophen tablets should not be used for an extended period of time.

DOSAGE AND ADMINISTRATION

- Tramadol hydrochloride and acetaminophen 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 of time consistent with individual patient treatment goals. Reserve titration to higher doses of tramadol hydrochloride and acetaminophen 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)
- 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 and acetaminophen tablets. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1,5.2)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with in a dosing range of two tablets every 4 to 6 as needed for pain relief, and at the lowest dosage necessary to achieve adequate analgesia. Titrate the dosage based upon the individual patient's response to their initial dose of tramadol hydrochloride and acetaminophen tablets; maximum of 8 tablets per day (2.3,5)
- 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 and acetaminophen tablets. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1,5.2, 5.3)
- Do not use with other acetaminophen- or tramadol-containing products. (2, 5.18)
- Severe Renal Impairment: Do not exceed 2 tablets every 12 hours. (2.4)
- Do not abruptly discontinue tramadol hydrochloride and acetaminophen tablets in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: tramadol hydrochloride 37.5 mg and acetaminophen 325 mg. (3)

CONTRAINDICATIONS

- Children younger than 12 years of age (4).
- Postoperative 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 absence of resuscitative equipment (4).
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4).
- Previous hypersensitivity to tramadol hydrochloride, acetaminophen, 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 OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (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 (5.10).
- 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 (5.11).
- **Risk of Suicide:** Do not prescribe for suicidal or addiction-prone patients (5.12).
- **Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Regularly evaluate closely, particularly during initiation and titration (5.13).
- **Adrenal Insufficiency:** If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid (5.14).
- **Severe Hypotension:** Regularly evaluate during dosage initiation and titration. Avoid use of tramadol hydrochloride and acetaminophen tablets in patients with circulatory shock (5.15).
- **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 and acetaminophen tablets in patients with impaired consciousness or coma (5.16).

-----ADVERSE REACTIONS-----

The most common incidence of treatment-emergent adverse events ($\geq 3.0\%$) in patients from clinical trials were constipation, diarrhea, nausea, somnolence, anorexia, dizziness, and sweating increased. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779) 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 and acetaminophen tablets because they may reduce analgesic effect of tramadol hydrochloride and acetaminophen 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: 9/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

Boxed warning

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

2.3 Initial Dosage

2.4 Dosage Modification in Patients with Renal Impairment

2.5 Safe Reduction or Discontinuation of Tramadol Hydrochloride and Acetaminophen Tablets

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse and Misuse

5.2 Life-Threatening Respiratory Depression

5.3 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

5.4 Neonatal Opioid Withdrawal Syndrome

5.5 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

5.6 Ultra-Rapid Metabolism and Other Risk Factors for Life-threatening Respiratory Depression in Children

5.7 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

- 5.8 Opioid-Induced Hyperalgesia and Allodynia
- 5.9 Hepatotoxicity
- 5.10 Serotonin Syndrome Risk
- 5.11 Increased Risk of Seizures
- 5.12 Suicide Risk
- 5.13 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
- 5.14 Adrenal Insufficiency
- 5.15 Severe Hypotension
- 5.16 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
- 5.17 Serious Skin Reactions
- 5.18 Risks of Use in Patients with Gastrointestinal Conditions
- 5.19 Anaphylaxis and Other Hypersensitivity Reactions
- 5.20 Increased Risk of Hepatotoxicity with Concomitant Use of Other Acetaminophen-containing Products
- 5.21 Withdrawal
- 5.22 Driving and Operating Machinery
- 5.23 Hyponatremia
- 5.24 Hypoglycemia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment
- 8.8 Sex

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Single-Dose Studies for Treatment of Acute Pain

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

Boxed warning

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

Addiction, Abuse, and Misuse

Because the use of tramadol hydrochloride and acetaminophen tablet exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing 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 and acetaminophen tablets, especially during initiation or following a dose increase. To reduce the risk of respiratory depression, proper dosing and titration of tramadol hydrochloride and acetaminophen tablets are essential [see *Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of tramadol hydrochloride and acetaminophen 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 and acetaminophen 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 (NOWS)

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 occurred following tonsillectomy and/or adenoidectomy, and 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 and acetaminophen tablets 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 and acetaminophen 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 and acetaminophen 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)*].

Hepatotoxicity

Tramadol hydrochloride and acetaminophen tablets contain tramadol hydrochloride and acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product [see *Warnings and Precautions (5.9)*].

1 INDICATIONS AND USAGE

Tramadol hydrochloride and acetaminophen tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Tramadol hydrochloride and acetaminophen tablets are indicated for short-term use of five days or less.

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 and acetaminophen tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- 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 and acetaminophen tablets should not be used for an extended period of time.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Tramadol hydrochloride and acetaminophen tablets are not approved for use for more than 5 days.

Do not exceed the recommended dose of tramadol hydrochloride and acetaminophen tablets. Do not coadminister tramadol hydrochloride and acetaminophen tablets with other tramadol or acetaminophen containing products [see *Warnings and Precautions (5.20)*].

- Tramadol hydrochloride and acetaminophen 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 of time 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 and acetaminophen 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.
- 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.
- 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 [see *Warnings and Precautions (5.1)*].
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with tramadol hydrochloride and acetaminophen tablets. Consider this risk when selecting an initial dose and when making dose adjustments [see *Warnings and Precautions (5)*].

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 and acetaminophen tablets [see *Warnings and Precautions (5.2), Patient Counseling Information (17)*].

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).

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 [see *Warnings and Precautions (5.1, 5.2, 5.3)*].

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

2.3 Initial Dosage

Initiate the treatment with tramadol hydrochloride and acetaminophen tablets is 2 tablets every 4 hours to 6 hours as needed for pain relief up to a maximum of 8 tablets per day, and at the lowest dosage necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of tramadol hydrochloride and acetaminophen tablets.

2.4 Dosage Modification in Patients with Renal Impairment

In patients with creatinine clearances of less than 30 mL/min, do not exceed 2 tablets every 12 hours.

2.5 Safe Reduction or Discontinuation of Tramadol Hydrochloride and Acetaminophen Tablets

Do not abruptly discontinue tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets, there are a variety of factors that should be considered, including the total daily dose of opioid (including tramadol hydrochloride and acetaminophen 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 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 opioids 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 use a gradual downward taper. 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, 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 for an extended period of time 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 and Precautions (5.21)*, *Drug Abuse and Dependence (9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tramadol Hydrochloride and Acetaminophen Tablets USP, 37.5 mg/325 mg are white, capsule-shaped, beveled-edge, biconvex, film-coated tablets, debossed "334" on one side and plain on other side.

4 CONTRAINDICATIONS

Tramadol hydrochloride and acetaminophen tablets are contraindicated for:

- all children younger than 12 years of age [see *Warnings and Precautions (5.6)*]
- post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see *Warnings and Precautions (5.6)*].

Tramadol hydrochloride and acetaminophen tablets are also contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions (5.2)*].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions (5.13)*].
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.18)*].
- Previous hypersensitivity to tramadol, acetaminophen, any other component of this product, or opioids [see *Warnings and Precautions (5.19)*].
- 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 and acetaminophen tablets contain tramadol, a Schedule IV controlled substance. As an opioid, tramadol hydrochloride and acetaminophen tablets expose 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 and acetaminophen 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 and acetaminophen tablets, and reassess all patients receiving tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets, but use in such patients necessitates intensive counseling about the risks and proper use of tramadol hydrochloride and acetaminophen 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 (5.2)*].

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing tramadol hydrochloride and acetaminophen 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 proper disposal of unused drug. 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 and acetaminophen tablets, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of tramadol hydrochloride and acetaminophen tablets are essential [*see Dosage and Administration (2)*]. Overestimating the tramadol hydrochloride and acetaminophen 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 and acetaminophen 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 Inform (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 and acetaminophen 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, 5.3), Patient Counseling Information (17)*].

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 and acetaminophen tablets with benzodiazepines and/or other CNS depressants, including alcohol (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 *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. Inform patients and caregivers of this potential interaction 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 (5.2)*]. Advise both patients and caregivers about the risks of respiratory depression and sedation when tramadol hydrochloride and acetaminophen 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 *Drug Interactions (7)*, *Patient Counseling Information (17)*].

5.4 Neonatal Opioid Withdrawal Syndrome

Use of tramadol hydrochloride and acetaminophen tablets for an extended period of time 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 an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations (8.1)* and *Patient Counseling Information (17)*].

5.5 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 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.6 Ultra-Rapid Metabolism 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 and acetaminophen tablets are contraindicated for all children younger than 12 years of age [see *Contraindications (4)*].
- Tramadol hydrochloride and acetaminophen 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 and acetaminophen 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 *Use in Specific Populations (8.4)*, *Overdosage (10)*].

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 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 and acetaminophen 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 and acetaminophen tablets [see *Use in Specific Populations (8.2)*].

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (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 (10)*]. Therefore, individuals who are ultra-rapid metabolizers should not use tramadol hydrochloride and acetaminophen tablets.

5.7 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 and acetaminophen tablets are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol hydrochloride and acetaminophen tablets requires 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 *Drug Interactions (7)*].

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

The concomitant use of tramadol hydrochloride and acetaminophen 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.

Evaluate patients receiving tramadol hydrochloride and acetaminophen tablets and any CYP2D6 inhibitor at frequent intervals 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 and acetaminophen tablets are used in conjunction with inhibitors of CYP2D6 [see *Drug Interactions (7)*].

Cytochrome P450 3A4 Interaction

The concomitant use of tramadol hydrochloride and acetaminophen 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 and acetaminophen 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.

Evaluate patients receiving tramadol hydrochloride and acetaminophen tablets and any CYP3A4 inhibitor or inducer at frequent intervals 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 and acetaminophen tablets are used in conjunction with inhibitors and inducers of CYP3A4 [see *Drug Interactions (7)*].

5.8 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. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see *Dependence (9.3)*]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. 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 moiety) [see *Dosage and Administration (2.5)*; *Warnings and Precautions (5.21)*].

5.9 Hepatotoxicity

Tramadol hydrochloride and acetaminophen tablets contain tramadol hydrochloride and acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of acetaminophen

per day, even if they feel well.

5.10 Serotonin Syndrome Risk

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, including tramadol hydrochloride and acetaminophen tablets, during concomitant use 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 *Drug Interactions (7)*]. 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 and acetaminophen tablets if serotonin syndrome is suspected.

5.11 Increased Risk of Seizures

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

Concomitant use of tramadol increases the seizure risk in patients taking: [see *Drug Interactions (7)*].

- Selective serotonin re-uptake inhibitors (SSRIs) and Serotonin-norepinephrine re-uptake inhibitors (SNRIs) antidepressants or anorectics,
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.),
- Other opioids,
- MAO inhibitors [see *Warnings and Precautions (5.10)*, *Drug Interactions (7)*]
- 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, metabolic disorders, alcohol and drug withdrawal, CNS infections).

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

5.12 Suicide Risk

- Do not prescribe tramadol hydrochloride and acetaminophen 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 (9)*].

- Prescribe tramadol hydrochloride and acetaminophen tablets with caution for patients with a 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 *Drug Interactions (7)*].
- Inform patients not to exceed the recommended dose and to limit their intake of alcohol [see *Dosage and Administration (2)*, *Warnings and Precautions (5.9, 5.3)*].

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

The use of tramadol hydrochloride and acetaminophen tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated [see *Contraindications (4)*].

Patients with Chronic Pulmonary Disease

Tramadol hydrochloride and acetaminophen tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of tramadol hydrochloride and acetaminophen tablets [see *Warnings and Precautions (5.2)*].

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, or altered clearance, compared to younger, healthier patients [see *Warnings and Precautions (5.2)*].

Regularly evaluate such patients, particularly when initiating and titrating tramadol hydrochloride and acetaminophen tablets and when tramadol hydrochloride and acetaminophen tablets are given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.5)*, *Drug Interactions (7)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.14 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one 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.

5.15 Severe Hypotension

Tramadol hydrochloride and acetaminophen tablets may cause severe hypotension including orthostatic 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 *Drug Interactions (7)*]. Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of tramadol hydrochloride and acetaminophen tablets. In patients with circulatory shock, tramadol hydrochloride and acetaminophen tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of tramadol hydrochloride and acetaminophen tablets in patients with circulatory shock.

5.16 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 and acetaminophen tablets may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Regularly evaluate such patients for signs of sedation and respiratory depression, particularly when initiating therapy with tramadol hydrochloride and acetaminophen tablets.

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

5.17 Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.18 Risks of Use in Patients with Gastrointestinal Conditions

Tramadol hydrochloride and acetaminophen tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see *Contraindications (4)*].

The tramadol in tramadol hydrochloride and acetaminophen tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.19 Anaphylaxis and Other Hypersensitivity Reactions

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to tramadol and other opioids may be at increased risk and therefore should not receive tramadol hydrochloride and acetaminophen tablets. If anaphylaxis or other hypersensitivity occurs, stop administration of tramadol hydrochloride and acetaminophen tablets immediately, discontinue tramadol hydrochloride and acetaminophen 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 (4)*].

There have been postmarketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue tramadol hydrochloride and acetaminophen tablets immediately and seek medical care if they experience these symptoms. Do not prescribe tramadol hydrochloride and acetaminophen tablets for patients with acetaminophen allergy.

5.20 Increased Risk of Hepatotoxicity with Concomitant Use of Other Acetaminophen-containing Products

Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, tramadol hydrochloride and acetaminophen tablets should not be used concomitantly with other acetaminophen containing products.

5.21 Withdrawal

Do not abruptly discontinue tramadol hydrochloride and acetaminophen tablets in a patient physically dependent on opioids. When discontinuing tramadol hydrochloride and acetaminophen tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol and acetaminophen in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see *Dosage and Administration (2.5)*, *Drug Abuse and Dependence (9.3)*].

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 and acetaminophen tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms [see *Drug Interactions (7)*].

5.22 Driving and Operating Machinery

Tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets and know how they will react to the medication [see *Patient Counseling Information (17)*].

5.23 Hyponatremia

Hyponatremia (serum sodium < 135 mmol/L) has been reported with the use of tramadol, and many cases are severe (sodium level < 120 mmol/L). Most cases of hyponatremia occurred in females over the age of 65 and within the first week of therapy. In some reports, hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Regularly evaluate patients for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment with tramadol hydrochloride and acetaminophen tablets, especially during initiation of

therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue tramadol hydrochloride and acetaminophen tablets [see *Dosage and Administration: Safe Reduction or Discontinuation of Tramadol Hydrochloride and Acetaminophen Tablets (2.5)*].

5.24 Hypoglycemia

Cases of tramadol-associated hypoglycemia have been reported, some resulting in hospitalization. In most cases, patients had predisposing risk factors (e.g. diabetes). If hypoglycemia is suspected, monitor blood glucose levels and consider drug discontinuation as appropriate [see *Dosage and Administration: Safe Reduction or Discontinuation of Tramadol Hydrochloride and Acetaminophen Tablets (2.5)*].

6 ADVERSE REACTIONS

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

- Opioid-Induced Hyperalgesia and Allodynia [See Warnings and Precautions (5.8)]
- Addiction, Abuse, and Misuse [see *Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions (5.2)*]
- Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children [see *Warnings and Precautions (5.6)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.4)*]
- Hepatotoxicity [see *Warnings and Precautions (5.9)*]
- Interactions with Benzodiazepines or Other CNS Depressants [see *Warnings and Precautions (5.3)*]
- Serotonin Syndrome [see *Warnings and Precautions (5.10)*]
- Seizures [see *Warnings and Precautions (5.11)*]
- Suicide [see *Warnings and Precautions (5.12)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.14)*]
- Severe Hypotension [see *Warnings and Precautions (5.15)*]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.18)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.19)*]
- Withdrawal [see *Warnings and Precautions (5.21)*]

6.1 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.

The most common incidence of treatment-emergent adverse events ($\geq 3.0\%$) in subjects from clinical trials was constipation, diarrhea, nausea, somnolence, anorexia, dizziness, and sweating increased.

Table 1 shows the incidence rate of treatment-emergent adverse events reported in $\geq 2.0\%$ of subjects over five days of tramadol hydrochloride and acetaminophen tablets use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 1 Incidence of Treatment-Emergent Adverse Events ($\geq 2.0\%$)

| Body System | Tramadol Hydrochloride And Acetaminophen Tablets (N=142) |
|--|---|
| Preferred Term | (%) |
| Gastrointestinal System Disorders | |
| Constipation | 6 |
| Diarrhea | 3 |
| Nausea | 3 |
| Dry Mouth | 2 |
| Psychiatric Disorders | |
| Somnolence | 6 |
| Anorexia | 3 |
| Insomnia | 2 |
| Central & Peripheral Nervous System | |
| Dizziness | 3 |
| Skin and Appendages | |
| Sweating Increased | 4 |
| Pruritus | 2 |
| Reproductive Disorders, Male* | |
| Prostatic Disorder | 2 |

* Number of males = 62

Incidence at least 1%, causal relationship at least possible or greater

The following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of tramadol hydrochloride and acetaminophen tablets.

Body as a Whole - Asthenia, fatigue, hot flushes

Central and Peripheral Nervous System - Dizziness, headache, tremor

Gastrointestinal System - Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting

Psychiatric Disorders - Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence

Skin and Appendages - Pruritus, rash, increased sweating

Selected Adverse events occurring at less than 1%

The following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in tramadol hydrochloride and acetaminophen tablets clinical trials.

Body as a Whole - Chest pain, rigors, syncope, withdrawal syndrome

Cardiovascular Disorders - Hypertension, aggravated hypertension, hypotension

Central and Peripheral Nervous System - Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paresthesias, stupor, vertigo

Gastrointestinal System - Dysphagia, melena, tongue edema

Hearing and Vestibular Disorders – Tinnitus

Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia

Liver and Biliary System – Hepatic function abnormal

Metabolic and Nutritional Disorders – Weight decrease

Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking

Red Blood Cell Disorders – Anemia

Respiratory System – Dyspnea

Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention

Vision Disorders – Abnormal vision

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of tramadol-containing products. 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 and acetaminophen tablets.

Androgen deficiency

Cases of androgen deficiency have occurred with use of opioids for an extended period of time [see *Clinical Pharmacology (12.2)*].

Hyperalgesia and Allodynia:

Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [see *Warnings and Precautions (5.8)*]

QT prolongation/torsade de pointes

Cases of QT prolongation and/or torsade de pointes have been reported with tramadol use. Many of these cases were reported in patients taking another drug labeled for QT prolongation, in patients with a risk factor for QT prolongation (e.g., hypokalemia), or in the overdose setting.

Eye disorders – miosis, mydriasis

Metabolism and nutrition disorders –

Hyponatremia: Cases of severe hyponatremia and/or SIADH have been reported in patients taking tramadol, most often in females over the age of 65, and within the first week of therapy [see *Warnings and Precautions (5.23)*].

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients [see *Warnings and Precautions (5.24)*].

Nervous system disorders – movement disorder, speech disorder

Psychiatric disorders – delirium

Other clinically significant adverse experiences previously reported with tramadol hydrochloride:

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure, and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures, and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

7 DRUG INTERACTIONS

Table 2 includes clinically significant interactions with tramadol hydrochloride and acetaminophen tablets.

Table 2 Clinically Significant Drug Interactions with Tramadol Hydrochloride and Acetaminophen Tablets

| Inhibitors of CYP2D6 | |
|-----------------------------|---|
| <i>Clinical Impact:</i> | The concomitant use of tramadol hydrochloride and acetaminophen tablets and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of tramadol hydrochloride and acetaminophen 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 |

| | |
|-----------------------------|---|
| | <p>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 <i>Clinical Pharmacology (12.3)</i>].</p> |
| <i>Intervention:</i> | <p>If concomitant use of a CYP2D6 inhibitor is necessary, evaluate patients at frequent intervals for adverse reactions including opioid withdrawal, seizures and serotonin syndrome.</p> <p>If a CYP2D6 inhibitor is discontinued, consider lowering tramadol hydrochloride and acetaminophen tablets dosage until stable drug effects are achieved. Evaluate patients at frequent intervals for adverse events including respiratory depression and sedation.</p> |
| <i>Examples</i> | Quinidine, fluoxetine, paroxetine and bupropion |
| Inhibitors of CYP3A4 | |
| <i>Clinical Impact:</i> | <p>The concomitant use of tramadol hydrochloride and acetaminophen tablets and CYP3A4 inhibitors can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of tramadol hydrochloride and acetaminophen tablets is achieved.</p> <p>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.</p> |
| <i>Intervention:</i> | <p>If concomitant use is necessary, consider dosage reduction of tramadol hydrochloride and acetaminophen tablets until stable drug effects are achieved. Evaluate patients at frequent intervals for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, consider increasing the tramadol hydrochloride and acetaminophen tablets dosage until stable drug effects are achieved and evaluate patients for signs</p> |

| | |
|---|---|
| | and symptoms of opioid withdrawal. |
| <i>Examples</i> | Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir) |
| CYP3A4 Inducers | |
| <i>Clinical Impact:</i> | <p>The concomitant use of tramadol hydrochloride and acetaminophen tablets and CYP3A4 inducers can decrease the plasma concentration of tramadol [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol.</p> <p>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.</p> |
| <i>Intervention:</i> | <p>If concomitant use is necessary, consider increasing the tramadol hydrochloride and acetaminophen tablets dosage until stable drug effects are achieved. Evaluate patients for signs of opioid withdrawal.</p> <p>If a CYP3A4 inducer is discontinued, consider tramadol hydrochloride and acetaminophen tablets dosage reduction and evaluate patients at frequent intervals for seizures and serotonin syndrome, and signs of respiratory depression and sedation.</p> <p>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 and acetaminophen tablets and carbamazepine is not recommended.</p> |
| <i>Examples</i> | Rifampin, carbamazepine, phenytoin |
| Benzodiazepines and Other Central Nervous System (CNS) Depressants | |
| <i>Clinical Impact:</i> | Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. |
| <i>Intervention:</i> | Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and |

| | |
|---|--|
| | <p>durations to the minimum required. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation) [see <i>Warnings and Precautions (5.3)</i>]. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 5.3)</i>].</p> |
| <i>Examples</i> | Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol. |
| Serotonergic Drugs | |
| <i>Clinical Impact:</i> | The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. |
| <i>Intervention:</i> | If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue tramadol hydrochloride and acetaminophen tablets if serotonin syndrome is suspected. |
| <i>Examples</i> | Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). |
| Monoamine Oxidase Inhibitors (MAOIs) | |
| <i>Clinical Impact:</i> | MAOI interactions with opioids may manifest as serotonin syndrome [see <i>Warnings and Precautions (5.9)</i>] or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.3)</i>]. |
| <i>Intervention:</i> | Do not use tramadol hydrochloride and acetaminophen tablets in patients taking MAOIs or within 14 days of stopping such treatment. |
| <i>Examples</i> | phenelzine, tranylcypromine, linezolid |
| Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics | |
| <i>Clinical Impact:</i> | May reduce the analgesic effect of tramadol hydrochloride and acetaminophen tablets and/or precipitate withdrawal symptoms. |
| <i>Intervention:</i> | Avoid concomitant use. |
| <i>Examples</i> | butorphanol, nalbuphine, pentazocine, buprenorphine |

| Muscle Relaxants | |
|------------------------------|---|
| <i>Clinical Impact:</i> | Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. |
| <i>Intervention:</i> | Because respiratory depression that may be greater than otherwise expected and decrease the dosage of tramadol hydrochloride and acetaminophen 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 <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.2, 5.3)</i>]. |
| Diuretics | |
| <i>Clinical Impact:</i> | Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. |
| <i>Intervention:</i> | Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed. |
| Anticholinergic Drugs | |
| <i>Clinical Impact:</i> | The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. |
| <i>Intervention:</i> | Evaluate patients for signs of urinary retention or reduced gastric motility when tramadol hydrochloride and acetaminophen tablets are used concomitantly with anticholinergic drugs. |
| Digoxin | |
| <i>Clinical Impact:</i> | Postmarketing surveillance of tramadol has revealed rare reports of digoxin toxicity. |
| <i>Intervention:</i> | Evaluate patients at frequent intervals for signs of digoxin toxicity and adjust dosage of digoxin as needed. |
| Warfarin | |
| <i>Clinical Impact:</i> | Postmarketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times. |
| <i>Intervention:</i> | Frequently reevaluate the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed. |

8 USE IN 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 [see *Warnings and Precautions (5.4)*]. Available data with tramadol hydrochloride and acetaminophen tablets in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, the combination of tramadol and acetaminophen decreased fetal weights and increased supernumerary ribs at 1.6 times the maximum recommended human daily dosage (MRHD). In separate animal reproduction studies, tramadol administration alone 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.

Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately 1.3 times the maximum human daily dose (MRHD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately 1.9 times the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

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

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 presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions (5.4)*].

Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing.

Labor or Delivery

Tramadol hydrochloride and acetaminophen tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. 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 and acetaminophen 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 and acetaminophen 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 and acetaminophen tablets, if any, on the later growth, development, and functional maturation of the child is unknown.

Data

Animal Data

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (1.6 times the maximum daily human tramadol/acetaminophen dosage), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. 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, 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 alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m² or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m² or 2.6 times the maximum daily human tramadol dosage).

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 1.3 times the maximum human daily dose (MHDD = 2.6 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or

skeletal malformations.

When pregnant rats received oral acetaminophen throughout gestation at doses of 1.9-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.5-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.7, 1.3, and 2.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Lactation

Risk Summary

Tramadol hydrochloride and acetaminophen 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 (12.1)*]. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with tramadol hydrochloride and acetaminophen tablets.

Clinical Considerations

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

Data

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

8.3 Females and Males of Reproductive Potential

Infertility

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)*, *Clinical Pharmacology (12.2)*, *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of tramadol hydrochloride and acetaminophen 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 adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol.

Because of the risk of life-threatening respiratory depression and death:

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

8.5 Geriatric Use

Elderly patients (65 years of age or older) may have increased sensitivity to tramadol. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

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 and acetaminophen tablets slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression [see *Warnings and Precautions (5.13)*].

Tramadol and acetaminophen are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

The pharmacokinetics and tolerability of tramadol hydrochloride and acetaminophen

tablets in patients with impaired hepatic function have not been studied. Based on information using tramadol immediate-release tablets in subjects with advanced cirrhosis of the liver, tramadol exposure was higher and half-lives of tramadol and active metabolite M1 were longer than in subjects with normal hepatic function [see *Clinical Pharmacology (12.3)*].

As tramadol and acetaminophen are both extensively metabolized by the liver, the use of tramadol hydrochloride and acetaminophen tablets in patients with hepatic impairment is not recommended [see *Warnings and Precautions (5.9)*].

8.7 Renal Impairment

The pharmacokinetics and tolerability of tramadol hydrochloride and acetaminophen tablets in patients with renal impairment has not been studied. Based on studies using tramadol extended-release tablets, the excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosage of tramadol hydrochloride and acetaminophen tablets not exceed 2 tablets every 12 hours. [see *Dosage and Administration (2.3)*]. The total amount of tramadol and M1 removed during a 4 hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone. Monitor closely for signs of respiratory depression, sedation, and hypotension.

8.8 Sex

Tramadol clearance was 20% higher in female subjects compared to males in four Phase 1 studies of tramadol hydrochloride and acetaminophen tablets in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Tramadol hydrochloride and acetaminophen tablet 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 (5.1)*].

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare 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 and acetaminophen tablets increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of tramadol hydrochloride and acetaminophen tablets with alcohol and other CNS 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 reevaluation 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 and acetaminophen tablets abuse include those with a history of prolonged use of any opioid, including products containing tramadol, those with a history of drug or alcohol abuse, or those who use tramadol hydrochloride and acetaminophen 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. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Tramadol hydrochloride and acetaminophen tablets, like other opioids, can be diverted for nonmedical 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 and Acetaminophen Tablets

Abuse of tramadol hydrochloride and acetaminophen tablets poses a risk of overdose and death. The risk is increased with concurrent use of tramadol hydrochloride and acetaminophen tablets with alcohol and/or other CNS depressants.

Tramadol hydrochloride and acetaminophen 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 a 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 a 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/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 use.

Do not abruptly discontinue tramadol hydrochloride and acetaminophen tablets in a patient physically dependent on opioids. Rapid tapering of tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of tramadol hydrochloride and acetaminophen 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 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 an opioid analgesic taper [*see Dosage and Administration (2.5), and Warnings and Precautions (5.21)*].

Infants born to mothers physically dependent on 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

Tramadol hydrochloride and acetaminophen tablet is a combination drug. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. The initial symptoms of tramadol overdose may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Acute overdose with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, QT prolongation, hypotension, partial or complete airway obstruction, atypical snoring, seizures, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Deaths due to overdose have been reported with abuse and misuse of tramadol [see *Warnings and Precautions (5.1)*]. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Acetaminophen

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose

A single or multiple drug overdose with tramadol and acetaminophen is a potentially lethal polydrug overdose. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, assisted ventilation, and other supportive measures should be employed as indicated. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of an overdose.

Tramadol

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 arrhythmias will require advanced life-support measures.

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 and acetaminophen 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 and acetaminophen tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. 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.

Acetaminophen

If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

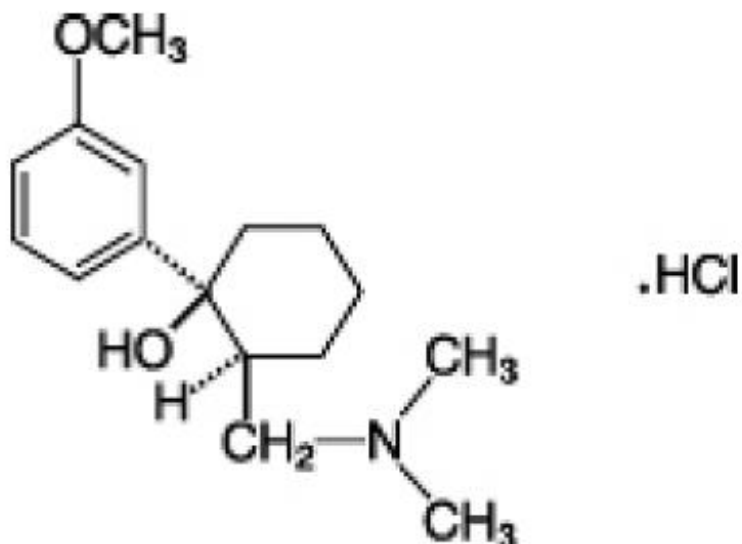
Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

11 DESCRIPTION

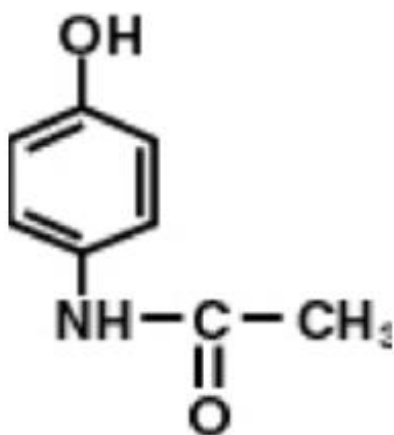
Tramadol hydrochloride and acetaminophen tablet, USP combines two analgesics, tramadol 37.5 mg and opioid agonist, acetaminophen 325 mg.

The chemical name for tramadol hydrochloride is (\pm)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride, USP is a white, crystalline powder.

The chemical name for acetaminophen is N-acetyl-p-aminophenol. Its structural formula is:



The molecular weight of acetaminophen is 151.16. Acetaminophen, USP is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

Each tramadol hydrochloride and acetaminophen tablets, USP intended for oral administration contains tramadol hydrochloride, 37.5 mg and acetaminophen, 325 mg. In addition, each tablet contains the following inactive ingredients: corn starch, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, sodium starch glycolate, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

The following information is based on studies of tramadol alone or acetaminophen alone, except where otherwise noted:

12.1 Mechanism of Action

Tramadol hydrochloride and acetaminophen tablets contain tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake, and acetaminophen. Although the mode of action of tramadol 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 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 [see *Clinical Pharmacology (12.3)*].

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.

Acetaminophen is a non-opioid, non-salicylate analgesic. The site and mechanism for the analgesic effect of acetaminophen has not been determined but is thought to primarily involve central actions.

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 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.

The effect of oral tramadol on the QTcF 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/day dose (1.5-fold the maximum immediate-release daily dose), the study demonstrated no significant effect on the QTcF interval.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see *Warnings and Precautions (5.12)*, *Adverse Reactions (6.2)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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, 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 (6.2)*].

Effects on the 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 modestly immunosuppressive.

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with extended-release 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 (2.1)*].

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 (2.1, 2.3)*].

12.3 Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

Absorption

The absolute bioavailability of tramadol from tramadol hydrochloride and acetaminophen tablets has not been determined. Tramadol has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. The mean peak plasma concentration of racemic tramadol and M1 after

administration of two tramadol hydrochloride and acetaminophen tablets occurs at approximately two and three hours, respectively, post-dose.

The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one tramadol hydrochloride and acetaminophen tablet are shown in Table 3. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Table 3 Summary of Mean (\pm SD) Pharmacokinetic Parameters of the (+)-and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose Of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

| Parameter ^a | (+)-Tramadol | | (-)-Tramadol | | (+)-M1 | | (-)-M1 | | acetaminophen | |
|--------------------------|--------------|-------|--------------|-------|--------|-------|--------|-------|---------------|-------|
| C _{max} (ng/mL) | 64.3 | (9.3) | 55.5 | (8.1) | 10.9 | (5.7) | 12.8 | (4.2) | 4.2 | (0.8) |
| t _{max} (h) | 1.8 | (0.6) | 1.8 | (0.7) | 2.1 | (0.7) | 2.2 | (0.7) | 0.9 | (0.7) |
| CL/F (mL/min) | 588 | (226) | 736 | (244) | - | - | - | - | 365 | (84) |
| t _{1/2} (h) | 5.1 | (1.4) | 4.7 | (1.2) | 7.8 | (3.0) | 6.2 | (1.6) | 2.5 | (0.6) |

^a For acetaminophen, C_{max} was measured as mcg/mL.

A single-dose pharmacokinetic study of tramadol hydrochloride and acetaminophen tablets in volunteers showed no drug interactions between tramadol and acetaminophen.

Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1, and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by coadministration with tramadol. Following single-or multiple-dose administration of tramadol hydrochloride and acetaminophen tablets, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Food Effect

When tramadol hydrochloride and acetaminophen tablets were administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentrations, and the extents of absorption, of tramadol and acetaminophen were not affected. The clinical significance of this difference is unknown.

Distribution

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

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relatively small portion (~20%) of acetaminophen is bound to plasma protein.

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 37.5 mg dose is 588 (226) mL/min for the (+) isomer and 736 (244) mL/min for the (-) isomer. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5 to 6 hours and 7 hours, respectively, after administration of tramadol hydrochloride and acetaminophen tablets. The apparent plasma elimination half-life of racemic tramadol increased to 7 hours to 9 hours upon multiple dosing of tramadol hydrochloride and acetaminophen tablets.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose dependent manner.

Metabolism

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response [see *Drug Interactions (7)*].

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, and 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. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline, and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

- a) conjugation with glucuronide;
- b) conjugation with sulfate; and
- c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a

lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Excretion

Approximately 30% of the tramadol dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations

Hepatic Impairment

Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of tramadol extended-release 100 mg. The exposure of (+)- and (-) tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)-M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of tramadol extended-release has not been studied in patients with severe hepatic impairment. After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function [see *Use in Specific Populations (8.6)*].

Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of tramadol extended-release 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CLcr: 50 mL/min to 80 mL/min) or moderate (CLcr: 30 mL/min to 50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20 % to 40% with increased severity of the renal impairment (from normal to mild and moderate). Tramadol extended-release has not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose [see *Dosage and Administration (2.4)*, *Use in Specific Populations (8.7)*].

Geriatric Population

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with tramadol hydrochloride and acetaminophen tablets, which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in the pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function [see *Use in Specific Populations (8.5)*].

Sex

Tramadol clearance was 20% higher in female subjects compared to males on four Phase 1 studies of tramadol hydrochloride and acetaminophen tablets in 50 male and 34 female healthy subjects.

Poor / Extensive Metabolizers, CYP2D6

The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower.

Drug Interaction Studies

CYP2D6 Inhibitors

In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Quinidine

Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg quinidine two hours before the administration of 100 mg tramadol extended release tablet. The results demonstrated that the exposure of tramadol increased 50% to 60% and the exposure of M1 decreased 50% to 60%. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism [see *Warnings and Precautions (5.6) and Drug Interactions (7)*].

Cimetidine

Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the tramadol hydrochloride and acetaminophen tablets dosage regimen is recommended.

CYP3A4 Inhibitors and Inducers

Tramadol is metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or CYP3A4 inducers, such as rifampin and St. John's Wort, with tramadol may affect the metabolism of tramadol leading to altered tramadol exposure [see *Warnings and Precautions (5.2, 5.7) and Drug Interactions (7)*].

Carbamazepine

Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Concomitant administration of tramadol and carbamazepine is not recommended.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility. Data on the individual components are described below.

Carcinogenesis

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.5 times the maximum recommended daily human dosage or MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water (1 times the MRHD).

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 1.2 times the maximum human daily dose (MHDD) of 2.6 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (1.1 times) or mice (1.9 times to 2.2 times the MHDD, based on a body surface area comparison).

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.

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive for induction of sister chromatid exchanges and chromosomal aberrations in *in vitro* assays using Chinese hamster ovary cells. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (2.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

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 1.6 and 2.4 times the MRHD [see *Use in Specific Populations* (8.3)].

In studies of acetaminophen conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

14 CLINICAL STUDIES

14.1 Single-Dose Studies for Treatment of Acute Pain

In single-dose studies in acute pain, two tablets of tramadol hydrochloride and acetaminophen tablets administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose. The onset of pain relief after tramadol hydrochloride and acetaminophen tablets was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after tramadol hydrochloride and acetaminophen tablets was longer than acetaminophen alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tramadol Hydrochloride and Acetaminophen Tablets USP, 37.5 mg/325 mg are white, capsule-shaped, beveled-edge, biconvex, film-coated tablets, debossed "334" on one side and plain on other side and are supplied as follows:

NDC 68382-334-01 in bottle of 100 tablets

NDC 68382-334-05 in bottle of 500 tablets

NDC 68382-334-10 in bottle of 1000 tablets

Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight container.

Store tramadol hydrochloride and acetaminophen tablets securely and dispose of properly [see *Patient Counseling Information (17)*].

17 PATIENT COUNSELING INFORMATION

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 and acetaminophen tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home [see *Warnings and Precautions (5.1, 5.21), Drug Abuse and Dependence (9.2)*]. Inform patients that leaving tramadol hydrochloride and acetaminophen 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 Drug Enforcement Administration (DEA)-registered collectors are available, instruct patients to dispose of tramadol hydrochloride and acetaminophen tablets by following these four steps:

- Mix tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share tramadol hydrochloride and acetaminophen tablets with others and to take steps to protect tramadol hydrochloride and acetaminophen 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 and acetaminophen 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 and Precautions (5.2)*].

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*].

Interactions with Benzodiazepines or Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if tramadol hydrochloride and acetaminophen tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see *Warnings and Precautions (5.3)*, *Drug Interactions (7)*].

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 and acetaminophen 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 *Dosage and Administration (2.3)*, *Warnings and Precautions (5.5)*].

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 (10)*].

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.

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

Advise caregivers that tramadol hydrochloride and acetaminophen tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children 12 to 18 years of age receiving tramadol hydrochloride and acetaminophen tablets to monitor for signs of respiratory depression [see *Warnings and Precautions (5.6)*].

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain [see *Warnings and Precautions (5.8)*; *Adverse Reactions (6.2)*].

Serotonin Syndrome

Inform patients that tramadol could cause a rare but potentially life-threatening condition, particularly during concomitant use with serotonergic drugs. Warn patients of the symptoms and signs of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they

are taking, or plan to take serotonergic medications [see *Warnings and Precautions (5.10)*].

MAOI Interaction

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

Seizures

Inform patients that tramadol hydrochloride and acetaminophen tablets may cause seizures with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol [see *Warnings and Precautions (5.11)*].

Important Administration Instructions

Instruct patients how to properly take tramadol hydrochloride and acetaminophen tablets [see *Dosage and Administration (2)*].

- Do not adjust the dose of tramadol hydrochloride and acetaminophen tablets without consulting with a physician or other healthcare provider.
- Do not take more than 4000 milligrams of acetaminophen per day and to call their healthcare provider if they took more than the recommended dose.

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue tramadol hydrochloride and acetaminophen tablets without first discussing a tapering plan with the prescriber [see *Dosage and Administration (2.5)*].

Driving or Operating Heavy Machinery

Inform patients that tramadol hydrochloride and acetaminophen tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see *Warnings and Precautions (5.22)*].

Constipation

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

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions (5.14)*].

Hypotension

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

[see Warnings and Precautions (5.15)].

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in tramadol hydrochloride and acetaminophen tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Warnings and Precautions (5.19), Adverse Reactions (6)].*

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that tramadol hydrochloride and acetaminophen tablets should not be used for more than 5 days and that use of for an extended period of time opioids such as tramadol hydrochloride and acetaminophen tablets, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. The patient should inform their healthcare provider if they have used opioids at any time during their pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)].*

Embryo-Fetal Toxicity

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

Lactation

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

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)].*

Maximum Daily Acetaminophen Use

Advise patients not to take more than 4,000 milligrams of acetaminophen per day and call their doctor if they have taken more than the recommended dose *[see Warnings and Precautions (5.9, 5.20)].*

Use with Other Acetaminophen-Containing Products

Advise patients not to take tramadol hydrochloride and acetaminophen tablets in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations *[see Warnings and Precautions (5.9, 5.20)].*

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured by:

Zydus Lifesciences Ltd.

Ahmedabad, India

Distributed by:

Zydus Pharmaceuticals (USA) Inc.

Pennington, NJ 08534

Rev.: 09/23

SPL MEDGUIDE

MEDICATION GUIDE
Tramadol Hydrochloride
(tram' a dol hye" droe klor' ide) and
Acetaminophen (a seet" a min' oh fen) Tablets, USP C-IV

Tramadol Hydrochloride and Acetaminophen Tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used for the short-term (five days or less) management of acute pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An 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.

Important information about Tramadol Hydrochloride and Acetaminophen Tablets:

- **Get emergency help or call 911 right away if you take too much tramadol hydrochloride and acetaminophen tablets (overdose) .** When you first start taking tramadol hydrochloride and acetaminophen tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Tramadol hydrochloride and acetaminophen tablets can cause severe drowsiness, breathing problems (respiratory depression), coma and death when taken with benzodiazepines or other medicines that depress consciousness.
- Never give anyone else your tramadol hydrochloride and acetaminophen tablets. They could die from taking it. Selling or giving away tramadol hydrochloride and acetaminophen tablets is against the law.
- Store tramadol hydrochloride and acetaminophen tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- Get emergency help right away if you take more than 4,000 mg of acetaminophen in 1 day. Taking tramadol hydrochloride and acetaminophen tablets with other products that contain acetaminophen can lead to serious liver problems and death.

Important Information Guiding Use in Pediatric Patients:

- Do not give tramadol hydrochloride and acetaminophen tablets to a child

younger than 12 years of age.

- Do not give tramadol hydrochloride and acetaminophen tablets to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets , if you have:

- Severe asthma, trouble breathing, or other lung problems.
- A bowel blockage or have narrowing of the stomach or intestines.
- An allergy to any of its ingredients (e.g., tramadol hydrochloride or acetaminophen).
- Taken a Monoamine Oxidase Inhibitor, MAOI, (medicine used for depression) within the last 14 days.

Before taking tramadol hydrochloride and acetaminophen 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:

- noticing your pain getting worse. If your pain gets worse after you take tramadol hydrochloride and acetaminophen tablets, do not take more of tramadol hydrochloride and acetaminophen tablets without first talking to your healthcare provider. Talk at you have increases, if you feel more sensitive to pain, or if you have new pain after tramadol hydrochloride and acetaminophen tablets.
- **Are pregnant or planning to become pregnant.** Use of tramadol hydrochloride and acetaminophen tablets for an extended period of time 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 and acetaminophen tablets with certain other medicines can cause serious side effects that could lead to death.

When taking tramadol hydrochloride and acetaminophen tablets:

- Do not change your dose. Take tramadol hydrochloride and acetaminophen

tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.

- For acute (short-term) pain, you may only need to take tramadol hydrochloride and acetaminophen tablets for a few days. You may have some tramadol hydrochloride and acetaminophen tablets left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused tramadol hydrochloride and acetaminophen tablets.
- Take your prescribed dose: 2 tablets every 4 hours to 6 hours as needed for pain relief for a maximum of 5 days. Do not take more than your prescribed dose and do not take more than 8 tablets per day. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking tramadol hydrochloride and acetaminophen tablets regularly, do not stop taking tramadol hydrochloride and acetaminophen tablets without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused tramadol hydrochloride and acetaminophen tablets by taking your drug to an authorized Drug Enforcement Administration (DEA)-registered collector or drug take-back program. If one is not available, you can dispose of tramadol hydrochloride and acetaminophen 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. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking Tramadol Hydrochloride and Acetaminophen Tablets DO NOT:

- Drive or operate heavy machinery, until you know how tramadol hydrochloride and acetaminophen tablets affect you. Tramadol hydrochloride and acetaminophen 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 and acetaminophen tablets may cause you to overdose and die.

The possible side effects of tramadol hydrochloride and acetaminophen tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. 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 and acetaminophen tablets. Call your healthcare provider 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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured by:
Zydus Lifesciences Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals (USA) Inc.
Pennington, NJ 08534

Rev.: 09/23

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

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 68382-334-01

Tramadol Hydrochloride and Acetaminophen Tablets USP, 37.5 mg/325 mg

100 Tablets

Rx only

Zydus

NDC 68382-334-01

Tramadol ^{IV}
Hydrochloride and
Acetaminophen
Tablets, USP

37.5 mg / 325 mg

334

Dispense the Medication Guide provided separately to each patient.

zydus
pharmaceuticals

100 TABLETS
Rx only

Each tablet contains:
Tramadol hydrochloride, USP 37.5 mg
Acetaminophen, USP 325 mg
Usual Dosage: See package insert for complete prescribing information.
Store at 20° to 25°C (68° to 77°F)
[See USP Controlled Room Temperature].
Dispense in a tight container with child-resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals (USA) Inc.
Pennington, NJ 08534

Rev: 09/17

TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN

tramadol hydrochloride and acetaminophen tablet, film coated

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:68382-334 |
| Route of Administration | ORAL | DEA Schedule | CIV |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|------------------------|----------|
| ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D) | ACETAMINOPHEN | 325 mg |
| TRAMADOL HYDROCHLORIDE (UNII: 9N7R477WCK) (TRAMADOL - UNII:39J1LGJ30J) | TRAMADOL HYDROCHLORIDE | 37.5 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|---|----------|
| STARCH, CORN (UNII: O8232NY3SJ) | |
| HYPROMELLOSES (UNII: 3NXW29V3WO) | |
| MAGNESIUM STEARATE (UNII: 70097M6I30) | |
| CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U) | |
| POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE) | |
| SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2) | |
| TALC (UNII: 7SEV7J4R1U) | |
| TITANIUM DIOXIDE (UNII: 15FIX9V2JP) | |

Product Characteristics

| | | | |
|-----------------|-------------------|---------------------|----------|
| Color | WHITE (WHITE) | Score | no score |
| Shape | CAPSULE (CAPSULE) | Size | 15mm |
| Flavor | | Imprint Code | 334 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|---|----------------------|--------------------|
| 1 | NDC:68382-334-01 | 100 in 1 BOTTLE; Type 0: Not a Combination Product | 10/15/2012 | |
| 2 | NDC:68382-334-05 | 500 in 1 BOTTLE; Type 0: Not a Combination Product | 10/15/2012 | |
| 3 | NDC:68382-334-10 | 1000 in 1 BOTTLE; Type 0: Not a Combination Product | 10/15/2012 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA090460 | 10/15/2012 | |

Labeler - Zydus Pharmaceuticals USA Inc. (156861945)

Registrant - Zydus Pharmaceuticals USA Inc. (156861945)

Establishment

| Name | Address | ID/FEI | Business Operations |
|----------------------------|---------|-----------|--|
| Zydus Lifesciences Limited | | 918596198 | ANALYSIS(68382-334) , MANUFACTURE(68382-334) |

Revised: 9/2023

Zydus Pharmaceuticals USA Inc.