210 mm

297 mm

SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the medicinal product

TRAMACET

2. Qualitative and quantitative declaration

Each tablet contains paracetamol 325 mg. and tramadol hydrochloride 37.5 mg

3. Pharmaceutical form

Oblong, biconvex, yellow film coated tablet with plain on both side.

4. Clinical particulars

4.1 Therapeutic indications

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

Limitations of Use TRAMACET tablets are indicated for short-term use of five days or less.

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Special Warnings and Precautions (4.4.1)], reserve TRAMACET 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.

4.2 Posology and method of administration

4.2.1 Important Dosage and Administration Instructions

- TRAMACET is not approved for use for more than 5 days.
- Do not exceed the recommended dose of TRAMACET. Do not co-administer TRAMACET with other tramadol or paracetamol containing products [see Special Warnings and Precautions (4.4.18)].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Special Warnings and Precautions (4.4.1)].
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Special Warnings and Precautions (4.4.1)].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with TRAMACET and adjust the dosage accordingly [see Special Warnings and Precautions (4.4.2)]

4.2.2 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 TRAMACET [see Special Warnings and Precautions (4.4.2), Patient Counseling Information (7)].

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 Special Warnings and Precautions (4.4.1, 4.4.2, 4.4.7)].

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

4.2.3 Initial Dosage

The initial dose of TRAMACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

4.2.4 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.

4.2.5 Safe Reduction or Discontinuation of TRAMACET

Do not abruptly discontinue TRAMACET 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 TRAMACET, there are a variety of factors that should be considered, including the dose of TRAMACET 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, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [see Special Warnings and Precautions (4.4.19), Drug Abuse and Dependence (4.10.3)]

4.2.6 Pediatric Use

The safety and effectiveness of TRAMACET in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol [see Special Warnings and Precautions (4.4.3)]. 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:

- TRAMACET is contraindicated for all children younger than age 12 years of age [see Contraindications (4.3)].
- TRAMACET is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4.3)].
- Avoid the use of TRAMACET 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.

4.2.7 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 co-administered with other agents that depress respiration. Titrate the dosage of TRAMACET slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Special Warnings and Precautions (4.4.2)].

Tramadol and paracetamol 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.

4.2.8 Renal Impairment

The pharmacokinetics and tolerability of TRAMACET 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 TRAMACET not exceed 2 tablets every 12 hours. [see Posology and Method of Administration (4.2.4)]. 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.

4.2.9 Hepatic Impairment

The pharmacokinetics and tolerability of TRAMACET 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 Pharmacokinetic Properties (5.2)].

As tramadol and paracetamol are both extensively metabolized by the liver, the use of TRAMACET in patients with hepatic impairment is not recommended [see Special Warnings and Precautions (4.4.6)]

4.2.10 Sex

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

4.3 Contraindications

TRAMACET is contraindicated for:

- all children younger than 12 years of age [see Special Warnings and Precautions (4.4.3)]
- post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Special Warnings and Precautions (4.4.3)].

TRAMACET is also contraindicated in patients with:

- Significant respiratory depression [see Special Warnings and Precautions (4.4.2)].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Special Warnings and Precautions (4.4.12)].
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see Special Warnings and Precautions (4.4.16)].
- Previous hypersensitivity to tramadol, paracetamol, any other component of this product, or opioids [see Special Warnings and Precautions (4.4.17)].
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days [see Interaction with other medicinal products and other forms of interactions (4.5)]

4.4 Special warnings and precautions

4.4.1 Addiction, Abuse and Misuse

TRAMACET contains tramadol. As an opioid, TRAMACET exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (4.10)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TRAMACET. 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 TRAMACET, and monitor all patients receiving TRAMACET 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 addiction or alcohol abuse) 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 TRAMACET, but use in such patients necessitates intensive counseling about the risks and proper use of TRAMACET along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.2)].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing TRAMACET. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see Patient Counseling Information (7)]. 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.

4.4.2 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 Overdose (4.9)]. Carbon dioxide (CO_2) 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 TRAMACET, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of TRAMACET.

To reduce the risk of respiratory depression, proper dosing and titration of TRAMACET are essential [see Posology and Method of Administration (4.2)]. Overestimating the TRAMACET 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 TRAMACET, 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 getting emergency medical help right away in the event of a known or suspected overdose [see Patient Counseling Information (7)].

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 Posology and Method Administration (4.2.5)].

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 TRAMACET. 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 getting emergency medical help, even if naloxone is administered [see Patient Counseling Information (7)].

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 Special Warnings and Precautions (4.4.1, 4.4.7), Patient Counseling Information (7)].

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

Life-threatening respiratory depression and death have occurred in children who received tramadol. 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 post-marketing 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:

- TRAMACET is contraindicated for all children younger than 12 years of age [see Contraindications (4.3)].
- TRAMACET is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4.3)].
- Avoid the use of TRAMACET 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 Pediatric Use (4.2.6), Overdose (4.9)].

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 TRAMACET 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 TRAMACET [see Lactation (4.6.2)].

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 Overdose (4.9)]. Therefore, individuals who are ultra-rapid metabolizers should not use TRAMACET.

4.4.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TRAMACET during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Pregnancy (4.6.1) and Patient Counseling Information (7)]

4.4.5 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 TRAMACET are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TRAMACET 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 Interaction with other medicinal products and other forms of interactions (4.5)].

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

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

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

Follow patients receiving TRAMACET and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when TRAMACET is used in conjunction with inhibitors of CYP2D6 [see Interaction with other medicinal products and other forms of interactions (4.5)].

Cytochrome P450 3A4 Interaction

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

Follow patients receiving TRAMACET and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when TRAMACET is used in conjunction with inhibitors and inducers of CYP3A4 [see Interaction with other medicinal products and other forms of interactions (4.5)].

4.4.6 Hepatotoxicity

TRAMACET contains tramadol hydrochloride and paracetamol. Paracetamol 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 paracetamol at doses that exceed 4,000 milligrams per day, and often involve more than one paracetamol-containing product. The excessive intake of paracetamol may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other paracetamol-containing products.

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

Instruct patients to look for paracetamol or APAP on package labels and not to use more than one product that contains paracetamol. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of paracetamol per day, even if they feel well.

4.4.7 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Interaction with other medicinal products and other forms of interactions (4.5)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.2)].

Advise both patients and caregivers about the risks of respiratory depression and sedation when TRAMACET is 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 Interaction with other medicinal products and other forms of interactions (4.5), Patient Counseling Information (7)]

4.4.8 Serotonin Syndrome Risk

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, including TRAMACET, 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 Interaction with other medicinal products and other forms of interactions (4.5)]. 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 TRAMACET if serotonin syndrome is suspected.

4.4.9 Increased Risk of Seizures

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing 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 Interaction with other medicinal products and other forms of interactions (4.5)].

- 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 Special Warnings and Precautions (4.4.8), Interaction with other medicinal products and other forms of interactions (4.5)]
- 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.

4.4.10 Suicide Risk

- Do not prescribe TRAMACET 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 (4.10)].
- Prescribe TRAMACET 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 Interaction with other medicinal products and other forms of interactions (4.5)].
- Inform patients not to exceed the recommended dose and to limit their intake of alcohol [see Posology and Method of Administration (4.2), Special Warnings and Precautions (4.4.6, 4.4.7)].

4.4.11 Adrenal Insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with TRAMACET should be considered.

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

The use of TRAMACET in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated [see Contraindications (4.3)].

Patients with Chronic Pulmonary Disease: TRAMACET-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 TRAMACET [see Special Warnings and Precautions (4.4.2)].

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 Special Warnings and Precautions (4.4.2)].

Monitor such patients closely, particularly when initiating and titrating TRAMACET and when TRAMACET is given concomitantly with other drugs that depress respiration [see Special Warnings and Precautions (4.4.7), Interaction with other medicinal products and other forms of interactions (4.5)]. Alternatively, consider the use of non-opioid analgesics in these patients

4.4.13 Severe Hypotension

TRAMACET 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 Interaction with other medicinal products and other forms of interactions (4.5)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of TRAMACET. In patients with circulatory shock, TRAMACET may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TRAMACET in patients with circulatory shock.

4.4.14 Risk 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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), TRAMACET may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with TRAMACET.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of TRAMACET in patients with impaired consciousness or coma.

4.4.15 Serious Skin Reactions

Rarely, paracetamol 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.

4.4.16 Risk of Use in Patients with Gastrointestinal Conditions

TRAMACET is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see Contraindications (4.3)].

The tramadol in TRAMACET may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Patients with disorders of the biliary tract or a history of biliary surgery should be monitored for potential development of acute pancreatitis, or worsening symptoms.

4.4.17 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 TRAMACET. If anaphylaxis or other hypersensitivity occurs, stop administration of TRAMACET immediately, discontinue TRAMACET 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 (4.3), Information for Patients (7)].

There have been postmarketing reports of hypersensitivity and anaphylaxis associated with the use of paracetamol. 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 TRAMACET immediately and seek medical care if they experience these symptoms. Do not prescribe TRAMACET for patients with paracetamol allergy.

4.4.18 Increased Risk of Hepatotoxicity with Concomitant Use of Other Paracetamol-containing Products

Due to the potential for paracetamol hepatotoxicity at doses higher than the recommended dose, TRAMACET should not be used concomitantly with other paracetamol containing products.

4.4.19 Withdrawal

Do not abruptly discontinue TRAMACET in a patient physically dependent on opioids. When discontinuing TRAMACET in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol and paracetamol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see Posology and Method of Administration (4.2.5), Drug Abuse and Dependence (4.10.3)].

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 TRAMACET. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms [see Interaction with other medicinal products and other forms of interactions (4.5)].

4.4.20 Driving and Operating Machinery

TRAMACET 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 TRAMACET and know how they will react to the medication [see Patient Counseling Information (7)]

4.4.21 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). Monitor for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment with TRAMACET, especially during initiation of therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue TRAMACET [see Posology and method of administration Safe Reduction or Discontinuation of TRAMACET (4.2.5)].

4.4.22 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 Posology and method of administration, Safe Reduction or Discontinuation of TRAMACET (4.2.5)].

4.4.23 Hyperprolactinemia

Long term opioid use may be associated with increased prolactin levels and decreased sex hormone levels. Symptoms may include galactorrhea, gynecomastia, impotence, decreased libido, infertility, or amenorrhea. If hyperprolactinemia is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with TRAMACET should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1 includes clinically significant interactions with TRAMACET.

Table 1: Clinically Significant Drug Interactions with TRAMACET

Inhibitors of CYP2D6	
Clinical Impact:	The concomitant use of TRAMACET 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 TRAMACET is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression [see Pharmacokinetic Properties (5.2)].
Intervention:	If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome. If a CYP2D6 inhibitor is discontinued, consider lowering TRAMACET dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine and bupropion
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of TRAMACET 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 TRAMACET is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease [see Pharmacokinetic Properties (5.2)], resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
Intervention:	If concomitant use is necessary, consider dosage reduction of TRAMACET until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the TRAMACET dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of TRAMACET and CYP3A4 inducers can decrease the plasma concentration of tramadol [see Pharmacokinetic Properties (5.2)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase [see Pharmacokinetic Properties (5.2)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.
Intervention:	If concomitant use is necessary, consider increasing the TRAMACET dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider TRAMACET dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of TRAMACET and carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Special Warnings and Precautions (4.4.7)]. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.1, 4.4.2, 4.4.7)].
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue TRAMACET if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome [see Special Warnings and Precautions (4.4.8)] or opioid toxicity (e.g., respiratory depression, coma) [see Special Warnings and Precautions (4.4.2)].
Intervention:	Do not use TRAMACET in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of TRAMACET and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of TRAMACET 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 Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.2, 4.4.7)].
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when TRAMACET is used concomitantly with anticholinergic drugs.
Digoxin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.
Intervention:	Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.
Warfarin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.
Intervention:	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Special Warnings and Precautions (4.4.4)]. Available data with TRAMACET 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 paracetamol 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 paracetamol. Treatment of pregnant rats with doses of paracetamol 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 paracetamol 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 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics 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 Special Warnings and Precautions (4.4.4)]

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

Labor or Delivery

TRAMACET is 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. TRAMACET is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including TRAMACET, 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.

0.83 for 40 women given tramadol during labor.

The effect of TRAMACET, 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 paracetamol. The tramadol/paracetamol combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/paracetamol (1.6 times the maximum daily human tramadol/paracetamol 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/m^2 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/m^2 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/m^2 or 2.6 times the maximum daily human tramadol dosage).

Studies in pregnant rats that received oral paracetamol 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 paracetamol 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 paracetamol 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% paracetamol 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.

4.6.2 Lactation

Risk Summary

TRAMACET is 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 Pharmacological Properties (5)]. 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 TRAMACET.

Clinical Considerations

If infants are exposed to TRAMACET 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 breastfeeding 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.

4.6.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Undesirable effects (4.8.2), Pharmacodynamic Properties (5.1), Preclinical Safety Data (5.3)].

4.7 Effects on ability to drive and use machines

See 4.4.20 Driving and Operating Machinery

4.8 Undesirable effects

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

- Addiction, Abuse, and Misuse [see Special Warnings and Precautions (4.4.1)]
- Life-Threatening Respiratory Depression [see Special Warnings and Precautions (4.4.2)]
- Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children [see Special Warnings and Precautions (4.4.3)]
- Neonatal Opioid Withdrawal Syndrome [see Special Warnings and Precautions (4.4.4)]
- Hepatotoxicity [see Special Warnings and Precautions (4.4.6)]
- Interactions with Benzodiazepines or Other CNS Depressants [see Special Warnings and Precautions (4.4.7)]
- Serotonin Syndrome [see Special Warnings and Precautions (4.4.8)]
- Seizures [see Special Warnings and Precautions (4.4.9)]
- Suicide [see Special Warnings and Precautions (4.4.10)]
- Adrenal Insufficiency [see Special Warnings and Precautions (4.4.11)]
- Severe Hypotension [see Special Warnings and Precautions (4.4.13)]
- Gastrointestinal Adverse Reactions [see Special Warnings and Precautions (4.4.16)]
- Hypersensitivity Reactions [see Special Warnings and Precautions (4.4.17)]
- Withdrawal [see Special Warnings and Precautions (4.4.19)]

4.8.1 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 (≥3.0%) in subjects from clinical trials was constipation, diarrhea, nausea, somnolence, anorexia, dizziness, and sweating increased.

Table 2 shows the incidence rate of treatment-emergent adverse events reported in ≥2.0% of subjects over five days of tramadol hydrochloride/paracetamol use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 2: Incidence of Treatment-Emergent Adverse Events (≥ 2.0%)

Body System Preferred Term	Tramadol hydrochloride/Paracetamol (N=142) (%)
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/Paracetamol

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/paracetamol 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

4.8.2 Post-marketing 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 TRAMACET.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see Pharmacodynamic Properties (5.1)].

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 Special Warnings and Precautions (4.4.21)].

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 Special Warnings and Precautions (4.4.22)].

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.

4.9 Overdose

Clinical Presentation

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

Tramadol

Acute overdosage 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 Special Warnings and Precautions (4.4.1)]. 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.

Paracetamol

In acute paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia also occur. Plasma paracetamol 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 paracetamol is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. 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.

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 techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose.

For clinically significant respiratory or circulatory depression secondary to 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 TRAMACET 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 TRAMACET, 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.

Paracetamol

If an paracetamol overdose is suspected, obtain a serum paracetamol 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 paracetamol 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 paracetamol level is below the lower line.

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; paracetamol 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.

4.10 Drug Abuse and Dependence

4.10.1 Controlled Substance

TRAMACET contains tramadol.

4.10.2 Abuse

TRAMACET contains tramadol, a substance with a high potential for abuse similar to other opioids and can be abused and is subject to misuse, addiction, and criminal diversion [see Special Warnings and Precautions (4.4.1)].

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

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

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

"Drug seeking" behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

TRAMACET, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of TRAMACET

TRAMACET is for oral use only. Abuse of TRAMACET poses a risk of overdose and death. The risk is increased with concurrent abuse of TRAMACET with alcohol and other central nervous system depressants.

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

4.10.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

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

Do not abruptly discontinue TRAMACET in a patient physically dependent on opioids. Rapid tapering of TRAMACET 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 opioids, gradually taper the dosage using a patient-specific plan that considers the following: the dose of the opioid the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see Posology and Method of Administration (4.2.5), Special Warnings and Precautions (4.4.19)].

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Pregnancy (4.6.1)]

5. Pharmacological properties

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

Mechanism of Action

TRAMACET contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake, and paracetamol. 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 Pharmacokinetic Properties (5.2)].

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.

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

5.1 Pharmacodynamic Properties

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 adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see Special Warnings and Precautions (4.4.11), Undesirable effects (4.8.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Undesirable effects (4.8.2)].

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 potent opioid agonists. The minimum effective analgesic concentration of tramadol for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [see Posology and Method of Administration (4.2.1)].

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 Posology and Method of Administration (4.2.1, 4.2.3)]

5.2 Pharmacokinetic Properties

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 TRAMACET tablets has not been determined. Tramadol has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of ULTRAM tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two TRAMACET tablets occurs at approximately two and three hours, respectively, post-dose.

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

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

Parameter*	(+)-Tramadol	(-)-Tramadol	(+)-M1	(-)-M1	paracetamol
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)

* For paracetamol, C_{max} was measured as mcg/mL.

A single-dose pharmacokinetic study of TRAMACET in volunteers showed no drug interactions between tramadol and paracetamol.

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 paracetamol occur within one hour and are not affected by co-administration with tramadol. Following single- or multiple-dose administration of TRAMACET, no significant change in paracetamol pharmacokinetics was observed when compared to paracetamol given alone.

Food Effect

When TRAMACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for paracetamol. However, peak plasma concentrations, and the extents of absorption, of tramadol and paracetamol 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.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of paracetamol 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 5-6 and 7 hours, respectively, after administration of TRAMACET. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of TRAMACET.

The half-life of paracetamol is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Paracetamol 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 Interaction with other medicinal products and other forms of interactions (4.5)].

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.

Paracetamol 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 paracetamol 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 paracetamol 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 Hepatic Impairment (4.2.8)].

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: 50-80 mL/min) or moderate (CLcr: 30-50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20-40% 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 Posology and Method of Administration (4.2.4), Renal Impairment (4.2.9)].

Geriatric Population

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with TRAMACET, 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 paracetamol in elderly patients with normal renal and hepatic function [see Geriatric Use (4.2.7)]

Sex

Tramadol clearance was 20% higher in female subjects compared to males on four Phase 1 studies of TRAMACET 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 1 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 50-60% and the exposure of M1 decreased 50-60%. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism [see Special Warnings and Precautions (4.45) and Interaction with other medicinal products and other forms of in teractions (4.5)].

Cimetidine

Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the TRAMACET 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 Special Warnings and Precautions (4.4.2 and 4.4.5) and Interactions with other medicinal products and other forms of interactions (4.5)]

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.

5.3 Preclinical Safety Data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and paracetamol) 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 paracetamol. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing paracetamol 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 (1.9-2.2 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.

Paracetamol was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, paracetamol tested positive for induction of sister chromatid exchanges and chromosomal aberrations in *in vitro* assays using Chinese hamster ovary cells. In the published literature, paracetamol 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 Females and Males of Reproductive Potential (4.6.3)].

In studies of paracetamol 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 paracetamol, 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 paracetamol near the upper limit of daily dosing.

Published studies in rodents report that oral paracetamol 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.

5.4 Clinical Studies

5.4.1 Single-Dose Studies for Treatment of Acute Pain

In single-dose studies in acute pain, two tablets of TRAMACET 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 TRAMACET was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after TRAMACET was longer than paracetamol alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

6. Pharmaceutical particulars

6.1 List of excipients

- Corn starch
- Microcrystalline cellulose
- Pregelatinized starch
- Sodium starch glycolate
- Magnesium stearate
- Purified water
- Opadry® Yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

TRAMACET is contained in blister pack (Aluminium-PVC) of 10 tablets into paper box of 3 packs

7. Marketing authorization holder

Manufactured by : POND CHEMICAL COMPANY LIMITED

1/18 Moo 4, Buengkamproi,

Lam Luk Ka, Pathumthani 12150

Distributed by : MASA LAB COMPANY LIMITED

Bangkok 10150, Thailand

Tel. (662) 971-6299 E-mail address : info@masalab.com

8. Marketing authorization number(s)

2A 15092/67 (NG)

9. Date of first authorization/ renewal of the authorization

27/12/2024

10. Date of revision of the text

6 June 2025

SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the medicinal product

TRAMACET

2. Qualitative and quantitative declaration

Each tablet contains paracetamol 325 mg. and tramadol hydrochloride 37.5 mg

3. Pharmaceutical form

Oblong, biconvex, yellow film coated tablet with plain on both side.

4. Clinical particulars

4.1 Therapeutic indications

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

Limitations of Use TRAMACET tablets are indicated for short-term use of five days or less.

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Special Warnings and Precautions (4.4.1)], reserve TRAMACET 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.

4.2 Posology and method of administration

4.2.1 Important Dosage and Administration Instructions

- TRAMACET is not approved for use for more than 5 days.
- Do not exceed the recommended dose of TRAMACET. Do not co-administer TRAMACET with other tramadol or paracetamol containing products [see Special Warnings and Precautions (4.4.18)].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Special Warnings and Precautions (4.4.1)].
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Special Warnings and Precautions (4.4.1)].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with TRAMACET and adjust the dosage accordingly [see Special Warnings and Precautions (4.4.2)]

4.2.2 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 TRAMACET [see Special Warnings and Precautions (4.4.2), Patient Counseling Information (7)].

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 Special Warnings and Precautions (4.4.1, 4.4.2, 4.4.7)].

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

4.2.3 Initial Dosage

The initial dose of TRAMACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

4.2.4 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.

4.2.5 Safe Reduction or Discontinuation of TRAMACET

Do not abruptly discontinue TRAMACET 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 TRAMACET, there are a variety of factors that should be considered, including the dose of TRAMACET 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, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [see Special Warnings and Precautions (4.4.19), Drug Abuse and Dependence (4.10.3)]

4.2.6 Pediatric Use

The safety and effectiveness of TRAMACET in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol [see Special Warnings and Precautions (4.4.3)]. 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.

of administration (4.2.2), Special Warnings and Precautions (4.4.2)].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing TRAMACET. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see Patient Counseling Information (7)]. 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.

4.4.2 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 Overdose (4.9)]. Carbon dioxide (CO_2) 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 TRAMACET, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of TRAMACET.

To reduce the risk of respiratory depression, proper dosing and titration of TRAMACET are essential [see Posology and Method of Administration (4.2)]. Overestimating the TRAMACET 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 TRAMACET, 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 getting emergency medical help right away in the event of a known or suspected overdose [see Patient Counseling Information (7)].

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 Posology and Method Administration (4.2.5)].

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 TRAMACET. 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 getting emergency medical help, even if naloxone is administered [see Patient Counseling Information (7)].

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 Special Warnings and Precautions (4.4.1, 4.4.7), Patient Counseling Information (7)].

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

Life-threatening respiratory depression and death have occurred in children who received tramadol. 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 post-marketing 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:

- TRAMACET is contraindicated for all children younger than 12 years of age [see Contraindications (4.3)].
- TRAMACET is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4.3)].
- Avoid the use of TRAMACET 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 Pediatric Use (4.2.6), Overdose (4.9)].

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 TRAMACET 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 TRAMACET [see Lactation (4.6.2)].

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 Overdose (4.9)]. Therefore, individuals who are ultra-rapid metabolizers should not use TRAMACET.

4.4.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TRAMACET during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Pregnancy (4.6.1) and Patient Counseling Information (7)]

4.4.5 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 TRAMACET are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TRAMACET requires

substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [see Special Warnings and Precautions (4.4.19), Drug Abuse and Dependence (4.10.3)]

4.2.6 Pediatric Use

The safety and effectiveness of TRAMACET in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol [see Special Warnings and Precautions (4.4.3)]. 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:

- TRAMACET is contraindicated for all children younger than age 12 years of age [see Contraindications (4.3)].
- TRAMACET is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4.3)].
- Avoid the use of TRAMACET 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.

4.2.7 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 co-administered with other agents that depress respiration. Titrate the dosage of TRAMACET slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Special Warnings and Precautions (4.4.2)].

Tramadol and paracetamol 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.

4.2.8 Renal Impairment

The pharmacokinetics and tolerability of TRAMACET 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 TRAMACET not exceed 2 tablets every 12 hours. [see Posology and Method of Administration (4.2.4)]. 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.

4.2.9 Hepatic Impairment

The pharmacokinetics and tolerability of TRAMACET 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 Pharmacokinetic Properties (5.2)].

As tramadol and paracetamol are both extensively metabolized by the liver, the use of TRAMACET in patients with hepatic impairment is not recommended [see Special Warnings and Precautions (4.4.6)]

4.2.10 Sex

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

4.3 Contraindications

TRAMACET is contraindicated for:

- all children younger than 12 years of age [see Special Warnings and Precautions (4.4.3)]
- post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Special Warnings and Precautions (4.4.3)].

TRAMACET is also contraindicated in patients with:

- Significant respiratory depression [see Special Warnings and Precautions (4.4.2)].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Special Warnings and Precautions (4.4.12)].
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see Special Warnings and Precautions (4.4.16)].
- Previous hypersensitivity to tramadol, paracetamol, any other component of this product, or opioids [see Special Warnings and Precautions (4.4.17)].
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days [see Interaction with other medicinal products and other forms of interactions (4.5)]

4.4 Special warnings and precautions

4.4.1 Addiction, Abuse and Misuse

TRAMACET contains tramadol. As an opioid, TRAMACET exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (4.10)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed TRAMACET. 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 TRAMACET, and monitor all patients receiving TRAMACET 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 TRAMACET, but use in such patients necessitates intensive counseling about the risks and proper use of TRAMACET along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see Posology and method or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see Overdose (4.9)]. Therefore, individuals who are ultra-rapid metabolizers should not use TRAMACET.

4.4.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TRAMACET during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Pregnancy (4.6.1) and Patient Counseling Information (7)]

4.4.5 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 TRAMACET are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with TRAMACET 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 Interaction with other medicinal products and other forms of interactions (4.5)].

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

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

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

Follow patients receiving TRAMACET and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when TRAMACET is used in conjunction with inhibitors of CYP2D6 [see Interaction with other medicinal products and other forms of interactions (4.5)].

Cytochrome P450 3A4 Interaction

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

Follow patients receiving TRAMACET and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when TRAMACET is used in conjunction with inhibitors and inducers of CYP3A4 [see Interaction with other medicinal products and other forms of interactions (4.5)].

4.4.6 Hepatotoxicity

TRAMACET contains tramadol hydrochloride and paracetamol. Paracetamol 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 paracetamol at doses that exceed 4,000 milligrams per day, and often involve more than one paracetamol-containing product. The excessive intake of paracetamol may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other paracetamol-containing products.

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

Instruct patients to look for paracetamol or APAP on package labels and not to use more than one product that contains paracetamol. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of paracetamol per day, even if they feel well.

4.4.7 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Interaction with other medicinal products and other forms of interactions (4.5)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.2)].

Advise both patients and caregivers about the risks of respiratory depression and sedation when TRAMACET is 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 Interaction with other medicinal products and other forms of interactions (4.5), Patient Counseling Information (7)]

4.4.8 Serotonin Syndrome Risk

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, including TRAMACET, 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 Interaction with other medicinal products and other forms of interactions (4.5)]. 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 TRAMACET if serotonin syndrome is suspected.

4.4.9 Increased Risk of Seizures

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing 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 Interaction with other medicinal products and other forms of interactions (4.5)].

- 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 Special Warnings and Precautions (4.4.8), Interaction with other medicinal products and other forms of interactions (4.5)]
- 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.

4.4.10 Suicide Risk

- Do not prescribe TRAMACET 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 (4.10)].
- Prescribe TRAMACET 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 Interaction with other medicinal products and other forms of interactions (4.5)].
- Inform patients not to exceed the recommended dose and to limit their intake of alcohol [see Posology and Method of Administration (4.2), Special Warnings and Precautions (4.4.6, 4.4.7)].

4.4.11 Adrenal Insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with TRAMACET should be considered.

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

The use of TRAMACET in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated [see Contraindications (4.3)].

Patients with Chronic Pulmonary Disease: TRAMACET-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 TRAMACET [see Special Warnings and Precautions (4.4.2)].

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 Special Warnings and Precautions (4.4.2)].

Monitor such patients closely, particularly when initiating and titrating TRAMACET and when TRAMACET is given concomitantly with other drugs that depress respiration [see Special Warnings and Precautions (4.4.7), Interaction with other medicinal products and other forms of interactions (4.5)]. Alternatively, consider the use of non-opioid analgesics in these patients

4.4.13 Severe Hypotension

TRAMACET 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 Interaction with other medicinal products and other forms of interactions (4.5)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of TRAMACET. In patients with circulatory shock, TRAMACET may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of TRAMACET in patients with circulatory shock.

4.4.14 Risk 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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), TRAMACET may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with TRAMACET.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of TRAMACET in patients with impaired consciousness or coma.

4.4.15 Serious Skin Reactions

Rarely, paracetamol 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.

4.4.16 Risk of Use in Patients with Gastrointestinal Conditions

TRAMACET is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see Contraindications (4.3)].

The tramadol in TRAMACET may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Patients with disorders of the biliary tract or a history of biliary surgery should be monitored for potential development of acute pancreatitis, or worsening symptoms.

4.4.17 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 TRAMACET. If anaphylaxis or other hypersensitivity occurs, stop administration of TRAMACET immediately, discontinue TRAMACET 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 (4.3), Information for Patients (7)].

There have been postmarketing reports of hypersensitivity and anaphylaxis associated with the use of paracetamol. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening

	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 TRAMACET is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease [see Pharmacokinetic Properties (5.2)], resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
Intervention:	If concomitant use is necessary, consider dosage reduction of TRAMACET until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the TRAMACET dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of TRAMACET and CYP3A4 inducers can decrease the plasma concentration of tramadol [see Pharmacokinetic Properties (5.2)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase [see Pharmacokinetic Properties (5.2)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.
Intervention:	If concomitant use is necessary, consider increasing the TRAMACET dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider TRAMACET dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of TRAMACET and carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Special Warnings and Precautions (4.4.7)]. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.1, 4.4.2, 4.4.7)].
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue TRAMACET if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome [see Special Warnings and Precautions (4.4.8)] or opioid toxicity (e.g., respiratory depression, coma) [see Special Warnings and Precautions (4.4.2)].
Intervention:	Do not use TRAMACET in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of TRAMACET and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of TRAMACET 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 Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.2, 4.4.7)].
Diuretics	

The tramadol in TRAMACET may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Patients with disorders of the biliary tract or a history of biliary surgery should be monitored for potential development of acute pancreatitis, or worsening symptoms.

4.4.17 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 TRAMACET. If anaphylaxis or other hypersensitivity occurs, stop administration of TRAMACET immediately, discontinue TRAMACET 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 (4.3), Information for Patients (7)].

There have been postmarketing reports of hypersensitivity and anaphylaxis associated with the use of paracetamol. 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 TRAMACET immediately and seek medical care if they experience these symptoms. Do not prescribe TRAMACET for patients with paracetamol allergy.

4.4.18 Increased Risk of Hepatotoxicity with Concomitant Use of Other Paracetamol-containing Products

Due to the potential for paracetamol hepatotoxicity at doses higher than the recommended dose, TRAMACET should not be used concomitantly with other paracetamol containing products.

4.4.19 Withdrawal

Do not abruptly discontinue TRAMACET in a patient physically dependent on opioids. When discontinuing TRAMACET in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol and paracetamol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see Posology and Method of Administration (4.2.5), Drug Abuse and Dependence (4.10.3)].

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 TRAMACET. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms [see Interaction with other medicinal products and other forms of interactions (4.5)].

4.4.20 Driving and Operating Machinery

TRAMACET 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 TRAMACET and know how they will react to the medication [see Patient Counseling Information (7)]

4.4.21 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). Monitor for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment with TRAMACET, especially during initiation of therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue TRAMACET [see Posology and method of administration Safe Reduction or Discontinuation of TRAMACET (4.2.5)].

4.4.22 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 Posology and method of administration, Safe Reduction or Discontinuation of TRAMACET (4.2.5)].

4.4.23 Hyperprolactinemia

Long term opioid use may be associated with increased prolactin levels and decreased sex hormone levels. Symptoms may include galactorrhea, gynecomastia, impotence, decreased libido, infertility, or amenorrhea. If hyperprolactinemia is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with TRAMACET should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1 includes clinically significant interactions with TRAMACET.

Table 1: Clinically Significant Drug Interactions with TRAMACET

Inhibitors of CYP2D6	
Clinical Impact:	The concomitant use of TRAMACET 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 TRAMACET is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression [see Pharmacokinetic Properties (5.2)].
Intervention:	If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome. If a CYP2D6 inhibitor is discontinued, consider lowering TRAMACET dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine and bupropion
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of TRAMACET 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
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of TRAMACET 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 Posology and method of administration (4.2.2), Special Warnings and Precautions (4.4.2, 4.4.7)].
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when TRAMACET is used concomitantly with anticholinergic drugs.
Digoxin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.
Intervention:	Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.
Warfarin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.
Intervention:	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Special Warnings and Precautions (4.4.4)]. Available data with TRAMACET 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 paracetamol 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 paracetamol. Treatment of pregnant rats with doses of paracetamol 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 paracetamol 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 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics 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 Special Warnings and Precautions (4.4.4)]

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

Labor or Delivery

TRAMACET is 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. TRAMACET is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including TRAMACET, 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.

0.83 for 40 women given tramadol during labor.

The effect of TRAMACET, 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 paracetamol.

The tramadol/paracetamol combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/paracetamol (1.6 times the maximum daily human tramadol/paracetamol 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/m^2 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/m^2 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/m^2 or 2.6 times the maximum daily human tramadol dosage).

Studies in pregnant rats that received oral paracetamol 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 paracetamol 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 paracetamol 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% paracetamol 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.

4.6.2 Lactation

Risk Summary

TRAMACET is 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 Pharmacological Properties (5)]. 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 TRAMACET.

Clinical Considerations

If infants are exposed to TRAMACET 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 breastfeeding 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.

4.6.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Undesirable effects (4.8.2), Pharmacodynamic Properties (5.1), Preclinical Safety Data (5.3)].

4.7 Effects on ability to drive and use machines

See 4.4.20 Driving and Operating Machinery

4.8 Undesirable effects

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

- Addiction, Abuse, and Misuse [see Special Warnings and Precautions (4.4.1)]
- Life-Threatening Respiratory Depression [see Special Warnings and Precautions (4.4.2)]
- Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children [see Special Warnings and Precautions (4.4.3)]
- Neonatal Opioid Withdrawal Syndrome [see Special Warnings and Precautions (4.4.4)]
- Hepatotoxicity [see Special Warnings and Precautions (4.4.6)]
- Interactions with Benzodiazepines or Other CNS Depressants [see Special Warnings and Precautions (4.4.7)]
- Serotonin Syndrome [see Special Warnings and Precautions (4.4.8)]
- Seizures [see Special Warnings and Precautions (4.4.9)]
- Suicide [see Special Warnings and Precautions (4.4.10)]
- Adrenal Insufficiency [see Special Warnings and Precautions (4.4.11)]
- Severe Hypotension [see Special Warnings and Precautions (4.4.13)]
- Gastrointestinal Adverse Reactions [see Special Warnings and Precautions (4.4.16)]
- Hypersensitivity Reactions [see Special Warnings and Precautions (4.4.17)]
- Withdrawal [see Special Warnings and Precautions (4.4.19)]

4.8.1 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

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 TRAMACET.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see Pharmacodynamic Properties (5.1)].

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 Special Warnings and Precautions (4.4.21)].

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 Special Warnings and Precautions (4.4.22)].

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.

4.9 Overdose

Clinical Presentation

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

Tramadol

Acute overdosage 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 Special Warnings and Precautions (4.4.1)]. 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.

Paracetamol

In acute paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia also occur. Plasma paracetamol 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 paracetamol is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. 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.

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 techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose.

For clinically significant respiratory or circulatory depression secondary to 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 TRAMACET 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 TRAMACET, 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.

Paracetamol

If an paracetamol overdose is suspected, obtain a serum paracetamol 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 paracetamol 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 paracetamol level is below the lower line.

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; paracetamol 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

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and Precautions (4.4.3)]
- Neonatal Opioid Withdrawal Syndrome [see Special Warnings and Precautions (4.4.4)]
- Hepatotoxicity [see Special Warnings and Precautions (4.4.6)]
- Interactions with Benzodiazepines or Other CNS Depressants [see Special Warnings and Precautions (4.4.7)]
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- Hypersensitivity Reactions [see Special Warnings and Precautions (4.4.17)]
- Withdrawal [see Special Warnings and Precautions (4.4.19)]

4.8.1 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 (≥3.0%) in subjects from clinical trials was constipation, diarrhea, nausea, somnolence, anorexia, dizziness, and sweating increased.

Table 2 shows the incidence rate of treatment-emergent adverse events reported in ≥2.0% of subjects over five days of tramadol hydrochloride/paracetamol use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 2: Incidence of Treatment-Emergent Adverse Events (≥ 2.0%)

Body System Preferred Term	Tramadol hydrochloride/Paracetamol (N=142) (%)
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/Paracetamol

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/paracetamol 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

4.8.2 Post-marketing 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.

antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Paracetamol

If an paracetamol overdose is suspected, obtain a serum paracetamol 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 paracetamol 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 paracetamol level is below the lower line.

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; paracetamol 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.

4.10 Drug Abuse and Dependence

4.10.1 Controlled Substance

TRAMACET contains tramadol.

4.10.2 Abuse

TRAMACET contains tramadol, a substance with a high potential for abuse similar to other opioids and can be abused and is subject to misuse, addiction, and criminal diversion [see Special Warnings and Precautions (4.4.1)].

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

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

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

"Drug seeking" behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

TRAMACET, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of TRAMACET

TRAMACET is for oral use only. Abuse of TRAMACET poses a risk of overdose and death. The risk is increased with concurrent abuse of TRAMACET with alcohol and other central nervous system depressants.

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

4.10.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

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

Do not abruptly discontinue TRAMACET in a patient physically dependent on opioids. Rapid tapering of TRAMACET 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 opioids, gradually taper the dosage using a patient-specific plan that considers the following: the dose of the opioid the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see Posology and Method of Administration (4.2.5), Special Warnings and Precautions (4.4.19)].

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Pregnancy (4.6.1)]

5. Pharmacological properties

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

Mechanism of Action

TRAMACET contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake, and paracetamol. 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 Pharmacokinetic Properties (5.2)].

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.

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

5.1 Pharmacodynamic Properties

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 adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see Special Warnings and Precautions (4.4.11), Undesirable effects (4.8.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Undesirable effects (4.8.2)].

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 potent opioid agonists. The minimum effective analgesic concentration of tramadol for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [see Posology and Method of Administration (4.2.1)].

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 Posology and Method of Administration (4.2.1, 4.2.3)]

5.2 Pharmacokinetic Properties

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 TRAMACET tablets has not been determined. Tramadol has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of ULTRAM tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two TRAMACET tablets occurs at approximately two and three hours, respectively, post-dose.

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

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

Parameter[a]	(+)-Tramadol	(-)-Tramadol	(+)-M1	(-)-M1	paracetamol
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)
$t_{½}$ (h)	5.1 (1.4)	4.7 (1.2)	7.8 (3.0)	6.2 (1.6)	2.5 (0.6)

[a] For paracetamol, C_{max} was measured as mcg/mL.

A single-dose pharmacokinetic study of TRAMACET in volunteers showed no drug interactions between tramadol and paracetamol.

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 paracetamol occur within one hour and are not affected by co-administration with tramadol. Following single- or multiple-dose administration of TRAMACET, no significant change in paracetamol pharmacokinetics was observed when compared to paracetamol given alone.

Food Effect

When TRAMACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for paracetamol. However, peak plasma concentrations, and the extents of absorption, of tramadol and paracetamol 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.

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 50-60% and the exposure of M1 decreased 50-60%. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism [see Special Warnings and Precautions (4.45) and Interaction with other medicinal products and other forms of in teractions (4.5)].

Cimetidine

Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the TRAMACET 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 Special Warnings and Precautions (4.4.2 and 4.4.5) and Interactions with other medicinal products and other forms of interactions (4.5)]

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.

5.3 Preclinical Safety Data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and paracetamol) 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 paracetamol. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing paracetamol 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 (1.9-2.2 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.

Paracetamol was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, paracetamol tested positive for induction of sister chromatid exchanges and chromosomal aberrations in *in vitro* assays using Chinese hamster ovary cells. In the published literature, paracetamol 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 Females and Males of Reproductive Potential (4.6.3)].

In studies of paracetamol 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 paracetamol, 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 paracetamol near the upper limit of daily dosing.

Published studies in rodents report that oral paracetamol 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.

5.4 Clinical Studies

5.4.1 Single-Dose Studies for Treatment of Acute Pain

In single-dose studies in acute pain, two tablets of TRAMACET 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 TRAMACET was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after TRAMACET was longer than paracetamol alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

6. Pharmaceutical particulars

6.1 List of excipients

- Corn starch
- Microcrystalline cellulose
- Pregelatinized starch

For paracetamol, C_{max} was measured as mcg/mL.

A single-dose pharmacokinetic study of TRAMACET in volunteers showed no drug interactions between tramadol and paracetamol.

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 paracetamol occur within one hour and are not affected by co-administration with tramadol. Following single- or multiple-dose administration of TRAMACET, no significant change in paracetamol pharmacokinetics was observed when compared to paracetamol given alone.

Food Effect

When TRAMACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for paracetamol. However, peak plasma concentrations, and the extents of absorption, of tramadol and paracetamol 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.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of paracetamol 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 5-6 and 7 hours, respectively, after administration of TRAMACET. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of TRAMACET.

The half-life of paracetamol is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Paracetamol 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 Interaction with other medicinal products and other forms of interactions (4.5)].

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.

Paracetamol 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 paracetamol 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 paracetamol 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 Hepatic Impairment (4.2.8)].

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: 50-80 mL/min) or moderate (CLcr: 30-50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20-40% 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 Posology and Method of Administration (4.2.4), Renal Impairment (4.2.9)].

Geriatric Population

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with TRAMACET, 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 paracetamol in elderly patients with normal renal and hepatic function [see Geriatric Use (4.2.7)]

Sex

Tramadol clearance was 20% higher in female subjects compared to males on four Phase 1 studies of TRAMACET 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

paracetamol near the upper limit of daily dosing.

Published studies in rodents report that oral paracetamol 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.

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- Sodium starch glycolate
- Magnesium stearate
- Purified water
- Opadry® Yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

TRAMACET is contained in blister pack (Aluminium-PVC) of 10 tablets into paper box of 3 packs

7. Marketing authorization holder

Manufactured by : POND CHEMICAL COMPANY LIMITED
1/18 Moo 4, Buengkamproi,
Lam Luk Ka, Pathumthani 12150
Distributed by : MASA LAB COMPANY LIMITED
Bangkok 10150, Thailand
Tel. (662) 971-6299 E-mail address : info@masalab.com

8. Marketing authorization number(s)

2A 15092/67 (NG)

9. Date of first authorization/ renewal of the authorization

27/12/2024

10. Date of revision of the text

6 June 2025