NRx

Paracetamol & Tramadol Hydrochloride Tablets I.P.

ULTRACET®

Tramadol Hydrochloride and Acetaminophen Tablets USP

ULTRACET® Semi

DOSAGE FORMS AND STRENGTHS

ULTRACET/ ULTRACET SEMI is available as a light yellow, film-coated, biconvex, capsule-shaped tablet.

ULTRACET is available as tablets for oral administration containing 37.5 mg tramadol hydrochloride and 325 mg paracetamol & ULTRACET SEMI is available as tablets for oral administration containing 18.75 mg tramadol hydrochloride and 162.5 mg acetaminophen.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

ULTRACET/ ULTRACET SEMI is indicated for the management of severe acute pain.

Dosage and Administration

Dosage - adults and children 16 years of age and over

ULTRACET/ ULTRACET SEMI should not be used for more than 5 days when used for the treatment of severe acute pain.

The maximum single dose of ULTRACET/ ULTRACET SEMI is 1 to 2 tablets every 4 to 6 hours as needed for pain relief, up to per day maximum equivalent to 300 mg tramadol hydrochloride and 2.6 g paracetamol (acetaminophen). The lowest effective dose should be used for the shortest period of time.

Treatment withdrawal

Do not stop use of ULTRACET/ ULTRACET SEMI abruptly. Withdrawal symptoms may be relieved by tapering the medication (see *Warnings and Precautions – Treatment Withdrawal*).

Special populations

Children below 16 years of age

The use of ULTRACET/ ULTRACET SEMI is contraindicated in children below 12 years of age (see *Contraindications*).

The safety and effectiveness of ULTRACET/ ULTRACET SEMI in children aged 12 to below 16 years of age has not been established (see *Contraindications and Warnings and Precautions - Other risk factors for life-threatening respiratory depression in children*).

Elderly (65 years of age and older)

No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥65 years of age and younger subjects.

Renal impairment

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET/ ULTRACET SEMI be increased not to exceed 2 tablets every 12 hours.

Hepatic impairment

The use of ULTRACET/ ULTRACET SEMI in patients with severe hepatic impairment is not recommended.

Administration

ULTRACET/ ULTRACET SEMI tablets are for oral administration. ULTRACET/ ULTRACET SEMI can be administered without regard to food.

Contraindications

ULTRACET/ ULTRACET SEMI is contraindicated:

- in all children younger than 12 years of age.
- in post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- in patients who have previously demonstrated hypersensitivity to tramadol, paracetamol (acetaminophen), any other component of this product or opioids.
- in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.
- in patients using monoamine oxidase inhibitors (MAOIs) concurrently or within the last 14 days.
- in patients with significant respiratory depression (see *Warnings and Precautions*).

Warnings and Precautions

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 serotonergic drugs including: selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or opioids.
Administration of tramadol may enhance the seizure risk in patients taking: monoamine oxidase inhibitors (MAOIs), neuroleptics or other drugs that reduce the seizure threshold.

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

Anaphylactic reactions
Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET/ ULTRACET SEMI.

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol.

Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

Respiratory depression
Patients with significant respiratory depression (see *Contraindications*) or acute, severe bronchial asthma are at increased risk of life-threatening respiratory depression when treated with opioids.

Administer ULTRACET/ ULTRACET SEMI cautiously in patients at risk for respiratory depression.

When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia) (see *Adverse Reactions*). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids. (see *Dosage and Administration, Treatment withdrawal; Warnings and Precautions, Treatment withdrawal*).

CYP2D6 ultra-rapid metabolism of tramadol

Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may result in higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. (see *Overdose- Symptoms and signs, Tramadol*). Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolizers (see *Pharmacokinetic Properties*). 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- Symptoms and signs, Tramadol*).

Other risk factors for life-threatening respiratory depression in children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see *Contraindications*). 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 (see *Contraindications*). Because of the risk of life-threatening respiratory depression and death, avoid the use of ULTRACET/ ULTRACET SEMI in adolescents younger than 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea 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 *Dosage and Administration and Overdose - Symptoms and signs, Tramadol*).

Use with Central Nervous System (CNS) depressants, including alcohol

The concomitant use of tramadol (an active ingredient in ULTRACET/ ULTRACET SEMI) with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. ULTRACET/ ULTRACET SEMI should be used with caution and in reduced dosages when administered to patients receiving CNS depressants. (See *Interactions*)

Increased intracranial pressure or head trauma

ULTRACET/ ULTRACET SEMI should be used with caution in patients with increased intracranial pressure or head injury.

Drug dependence and potential for abuse

ULTRACET/ ULTRACET SEMI contains tramadol as an active ingredient. A portion of the analgesic effect of ULTRACET/ ULTRACET SEMI is attributable to the binding of the active ingredient, tramadol, to the mu-opioid receptor. Upon repeated administration of opioids, tolerance, physical dependence, and psychological dependence may develop, even at recommended dosages. Assess each patient's risk for opioid dependence and abuse prior to prescribing ULTRACET/ ULTRACET SEMI and monitor all patients receiving ULTRACET/ ULTRACET SEMI for development of these behaviors. 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).

ULTRACET/ ULTRACET SEMI should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids.

Increased risk of hepatotoxicity with alcohol use

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol (acetaminophen) use.

Treatment withdrawal

Withdrawal symptoms may occur if ULTRACET/ ULTRACET SEMI is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus, and unusual CNS symptoms have also been very rarely reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

Use with serotonergic drugs

Use ULTRACET/ ULTRACET SEMI with great caution in patients taking serotonergic drugs including SSRIs. Concomitant use of tramadol with serotonergic drugs including SSRI's increases the risk of adverse events, including seizure and serotonin syndrome (see *Interactions*).

Renal impairment

ULTRACET/ ULTRACET SEMI has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET/ ULTRACET SEMI be increased not to exceed 2 tablets every 12 hours.

Hepatic impairment

The use of ULTRACET/ ULTRACET SEMI in patients with severe hepatic impairment is not recommended

Serious skin reactions

Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients

receiving paracetamol (acetaminophen). 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.

Hyponatremia

Hyponatremia has been reported very rarely with the use of ULTRACET/ ULTRACET SEMI, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia. In some reports, this hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of ULTRACET/ ULTRACET SEMI and appropriate treatment (e.g. fluid restriction). During ULTRACET/ ULTRACET SEMI treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

Gastrointestinal conditions

Patients with disorders of the biliary tract or a history of biliary surgery should be monitored for potential development of acute pancreatitis.

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 ULTRACET/ ULTRACET SEMI should be considered.

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 ULTRACET/ ULTRACET SEMI should be considered.

Precautions general

The recommended dose of ULTRACET/ ULTRACET SEMI should not be exceeded.

ULTRACET/ ULTRACET SEMI should not be co-administered with other tramadol or paracetamol (acetaminophen) containing products.

Interactions

Based on its pharmacodynamic and pharmacokinetic properties, tramadol and paracetamol (acetaminophen) exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations and lists of examples are described below. These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is co-administered with tramadol and paracetamol (acetaminophen) be consulted for information

related to interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Table 1. Drug Interactions with ULTRACET/ ULTRACET SEMI

Inhibitors of CYP2D6	
Mechanism:	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical Impact:	The concomitant use of ULTRACET/ ULTRACET SEMI 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 ULTRACET/ ULTRACET SEMI 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 an inhibitor of CYP2D6, 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 *Pharmacological Properties – Pharmacokinetic properties*).
Intervention:	If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see *Warnings and Precautions – CYP2D6 ultra rapid metabolism of tramadol*). If an inhibitor of CYP2D6 is discontinued, consider lowering ULTRACET/ ULTRACET SEMI dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion
Inhibitors of CYP3A4	
Mechanism:	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical Impact:	The concomitant use of ULTRACET/ ULTRACET SEMI and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. After stopping an inhibitor of CYP3A4, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, 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 ULTRACET/ ULTRACET SEMI until stable drug effects are achieved. 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 ULTRACET/ ULTRACET SEMI is achieved. If an inhibitor of CYP3A4 is discontinued, consider increasing the ULTRACET/ ULTRACET SEMI 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	
Mechanism:	Enzyme induction resulting in increased rate of metabolism of tramadol.
Clinical Impact:	The concomitant use of ULTRACET/ ULTRACET SEMI and an inducer of CYP3A4 can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping an inducer of CYP3A4, as the effects of the inducer decline, the tramadol plasma concentration will increase, 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 ULTRACET/ ULTRACET SEMI dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If an inducer of CYP3A4 is discontinued, consider ULTRACET/ ULTRACET SEMI dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, an inducer of CYP3A4, 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 ULTRACET/ ULTRACET SEMI and carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants including alcohol	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	The concomitant use of tramadol with central nervous system depressants, such as benzodiazepines and other sedatives/hypnotics, anesthetic agents, phenothiazines, tranquilizers, opioids or alcohol, may produce additive CNS depressant effects, such as profound sedation and respiratory depression. If concomitant use of ULTRACET/ ULTRACET SEMI with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression. Due to additive pharmacodynamic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see *Warnings and Precautions*).
Examples:	Benzodiazepines and other sedatives/hypnotics, tranquilizers, muscle relaxants, general anesthetics, other opioids, alcohol.
Serotonergic Drugs	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	Concomitant use of tramadol with serotonergic drugs increases the risk of adverse events, including seizures and serotonin syndrome.
Intervention:	Use caution when administering ULTRACET/ ULTRACET SEMI in patients taking serotonergic drugs and monitor for signs of adverse events. Discontinue ULTRACET/ ULTRACET SEMI 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 and trazodone) and some muscle relaxants (e.g. cyclobenzaprine, metaxalone).
Monoamine Oxidase Inhibitors (MAOIs)	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical Impact:	The concomitant use of ULTRACET/ ULTRACET SEMI with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see *Contraindications*). MAOI interactions with opioids may manifest as serotonin syndrome (see *Warnings and Precautions – Use withserotonergic drugs*) or opioid toxicity (e.g., respiratory depression, coma) (see *Warnings and Precautions – Respiratory depression*).
Intervention:	Do not use ULTRACET/ ULTRACET SEMI in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Warfarin	
Clinical Impact:	As medically appropriate, periodic evaluation of prothrombin time should be performed when ULTRACET/ ULTRACET SEMI and these agents are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients. Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times. There have been several reports that suggest that paracetamol (acetaminophen) may produce hypoprothrombinemia when administered with warfarin-like compounds.
Intervention:	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.
Flucloxacillin	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	High anion gap metabolic acidosis (HAGMA) from pyroglutamic acid (5-oxoprolinemia) has been reported with concomitant use of therapeutic doses of paracetamol (acetaminophen) and flucloxacillin. Patients reported to be most at risk are elderly females with underlying disease such as sepsis, renal function abnormality, and malnutrition. Most patients improve after stopping one or both of the drugs.
Intervention:	Caution should be taken when flucloxacillin is used concomitantly with paracetamol (acetaminophen) as concurrent intake has been associated with HAGMA, especially in patients with risk factors. Discontinue ULTRACET/ ULTRACET SEMI and/or flucloxacillin if HAGMA is suspected
Cimetidine	
Clinical Impact:	Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

Pregnancy, Breast-feeding and Fertility

Pregnancy

Tramadol has been shown to cross the placenta.

There are no adequate and well-controlled studies in pregnant women.

Safe use in pregnancy has not been established.

The use of opioids during childbirth might result in respiratory depression in the newborn infant.

Prolonged use of ULTRACET/ ULTRACET SEMI, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

Breast-feeding

ULTRACET/ ULTRACET SEMI is not recommended for breast-feeding mothers because its safety in infants and newborns has not been studied.

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 breast-feeding infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby breast-feeding from an ultra-rapid metabolizer mother taking ULTRACET/ ULTRACET SEMI could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breast-feeding is not recommended during treatment with ULTRACET/ ULTRACET SEMI.

Fertility

The effect of tramadol or tramadol / paracetamol (acetaminophen) combination on human fertility has not been evaluated.

Effects on Ability to Drive and Use Machines

ULTRACET/ ULTRACET SEMI may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that have been considered to be reasonably causally associated with the use of tramadol hydrochloride / paracetamol (acetaminophen) based on a comprehensive assessment of the available adverse event information. A causal relationship with tramadol hydrochloride / paracetamol (acetaminophen) cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of ULTRACET/ ULTRACET SEMI was evaluated in 3,175 patients, 16 to 90 years of age, who participated in a total of 21 clinical trials of which 20 were double-blind, controlled (i.e., placebo or active, or both) and 1 was open-label with no control group. These 20 double-blind, controlled trials comprised 11 multiple-dose and 9 single-dose. The duration of treatment ranged from one dose to up to 23 months. All patients received at least one dose of ULTRACET/ ULTRACET SEMI and provided safety data.

Placebo-controlled double-blind data – adverse reactions reported at ≥1% incidence.

Sixteen of the 21 clinical trials were double-blind, placebo-controlled trials with a duration of treatment

ranging from one dose to 91 days. Adverse reactions determined from all 21 clinical trials and reported in the 16 double-blind placebo controlled clinical trials for ≥1% of ULTRACET/ ULTRACET SEMI-treated patients (N=1,669) and with an incidence greater than the rate in placebo-treated patients (N=1,531), are shown in Table 2. The most commonly occurring adverse reactions from the 16 placebo-controlled trials (>5% of patients) were nausea, dizziness, vomiting, headache, somnolence, and constipation.

Table 2. Adverse Reactions Reported by ≥1% of ULTRACET/ ULTRACET SEMI -treated Patients and With an Incidence Greater Than Placebo in 16 Double-blind, Placebo-controlled Clinical Trials of ULTRACET/ ULTRACET SEMI

	ULTRACET/ ULTRACET SEMI % (N=1,669)	**Placebo % (N=1,531)**
Metabolism and nutrition disorders		
Decreased appetite	1.4	0.3
Psychiatric disorders		
Insomnia	2.0	1.0
Nervous system disorders		
Dizziness	9.5	3.3
Headache	8.1	7.5
Somnolence	7.3	2.2
Gastrointestinal disorders		
Nausea	17.7	7.9
Vomiting	8.5	3.9
Constipation	6.8	2.6
Dry mouth	3.2	0.5
Diarrhea	2.2	1.8
Dyspepsia	1.4	1.0
Abdominal pain	1.4	1.0
Skin and subcutaneous tissue disorders		
Pruritus	3.7	0.8
Hyperhidrosis	2.3	0.4
General disorders and administration site conditions		
Fatigue	2.9	0.9

Placebo-controlled, comparator-controlled, and open-label clinical trial data – adverse reactions reported by ≥1% of ULTRACET/ ULTRACET SEMI-treated patients

Adverse reactions not reported in Table 2 that were reported by ≥1% of ULTRACET/ ULTRACET SEMI-treated patients (N=3,175) in the 21 clinical trials of ULTRACET/ ULTRACET SEMI are shown in Table 3. All patients received at least one dose of ULTRACET/ ULTRACET SEMI and provided safety data.

Table 3. Adverse Reactions Reported by ≥1% of ULTRACET/ ULTRACET SEMI-treated Patients in 21 Clinical Trials of ULTRACET/ ULTRACET SEMI that are not Listed in Table 2

System Organ Class Adverse Reaction	**ULTRACET/ ULTRACET SEMI** **%** **(N=3,175)**
Psychiatric disorders	
Depression	1.2
Vascular disorders	
Hot flush	1.0
Gastrointestinal disorders	
Abdominal discomfort	1.5
Flatulence	1.1
Skin and subcutaneous tissue disorders	
Rash	1.6

Placebo-controlled, comparator-controlled, and open-label study data – adverse reactions reported at <1% incidence of ULTRACET/ ULTRACET SEMI-treated Patients

Adverse reactions not reported above, which were reported by <1% of ULTRACET/ ULTRACET SEMI-treated patients (N=3,175) in the above clinical trial dataset are shown in Table 4.

Table 4. Adverse Reactions Reported by <1% of ULTRACET/ ULTRACET SEMI-treated Patients in 21 Clinical Trials of ULTRACET/ ULTRACET SEMI

System Organ Class Adverse Reaction	ULTRACET/ ULTRACET SEMI % (N=3,175)
Immune system disorders	
Urticaria	0.31
Hypersensitivity	0.19
Metabolism and nutrition disorders	
Hypoglycemia	0.06
Psychiatric disorders	
Anxiety	0.88
Nervousness	0.79
Agitation	0.41
Euphoric mood	0.31
Libido decreased	0.31
Sleep disorder	0.28
Confusional state	0.22
Disorientation	0.22
Irritability	0.22
Abnormal dreams[a]	0.38
Drug Abuse	0.03
Hallucination	0.03
Withdrawal syndrome	0.03
Nervous system disorders	
Migraine	0.82
Lethargy	0.76
Hypoesthesia	0.69
Tremor	0.60
Paresthesia	0.47
Disturbance in attention	0.28
Syncope	0.28
Memory impairment	0.25
Psychomotor hyperactivity	0.19
Sedation	0.16
Amnesia	0.09
Cognitive disorder	0.03
Seizure	0.03
Eye disorders	
Vision blurred	0.35
Visual impairment	0.16
Miosis	0.03
Ear and labyrinth disorders	
Vertigo	0.66
Tinnitus	0.63
Ear discomfort	0.16
Cardiac disorders	
Palpitations	0.31
Tachycardia	0.13
Vascular disorders	
Hypertension	0.91
Hypotension	0.06
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	0.44
Dry throat	0.16
Hepatobiliary disorders	
Hepatic enzyme increased[b]	0.41
Skin and subcutaneous tissue disorders	
Pruritus generalized	0.76

System Organ Class Adverse Reaction	ULTRACET/ ULTRACET SEMI % (N=3,175)
Cold sweat	0.22
Renal and urinary disorders	
Micturition disorder[c]	0.85
Reproductive system and breast disorders	
Erectile dysfunction	0.38
General disorders and administration site conditions	
Asthenia	0.94
Chest pain	0.50
Feeling abnormal	0.47
Chills	0.25
Chest discomfort	0.22
Malaise	0.22
Drug withdrawal syndrome	0.19
Thirst	0.19
Feeling jittery	0.13
Feeling hot	0.09
Investigations	
Weight decreased	0.50
Blood creatinine increased	0.13

[a] Abnormal dreams may include the following adverse events as applicable: nightmare and/or abnormal dreams

[b] Hepatic enzyme increased may include the following adverse events as applicable: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, alanine aminotransferase abnormal, and/or hepatic enzyme abnormal

[c] Micturition disorder may include the following adverse events as applicable: dysuria, urinary retention, urinary hesitation, and/or micturition frequency decreased

Adverse reactions reported with tramadol only

Table 5 lists the adverse reactions relating to the active moiety, tramadol, that were identified in clinical trials and/or postmarketing experience with tramadol but were not reported by any ULTRACET/ ULTRACET SEMI-treated patients in the ULTRACET/ ULTRACET SEMI clinical trials.

Table 5. Adverse Reactions Identified in Clinical Trials and/or Postmarketing Experience With Tramadol

System Organ Class Adverse Reaction
Immune system disorders
Anaphylactic reaction
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Psychiatric disorders
Affect lability
Delirium
Suicidal ideation
Nervous system disorders
Hypertonia
Movement disorder
Serotonin syndrome
Speech disorder
Eye disorders
Mydriasis
Vascular disorders
Orthostatic hypotension
Hepatobiliary disorders
Hepatitis
General disorders and administration site conditions
Gait disturbance
Investigations
Prothrombin time prolonged

Postmarketing data

In addition to the adverse reactions reported during clinical trials and listed above, the following adverse reactions have been reported during postmarketing experience (Table 6). The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very rare	<1/10000
Not known	(cannot be estimated from the available data)

In Table 6, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 6. Adverse Reactions Identified During Postmarketing Experience with ULTRACET/ ULTRACET SEMI by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class Frequency: Adverse Reaction
Metabolism and nutrition disorders
Not known, Hyponatremia/syndrome of inappropriate antidiuretic hormone
Immune system disorders
Very rare, Fixed eruption

Overdose

Accidental ingestion

Accidental ingestion of tramadol can result in respiratory depression and seizures due to an overdose of tramadol. Respiratory depression and seizures have been reported in a child following ingestion of a single tablet.

Fatalities due to tramadol overdose have also been reported.

Symptoms and signs

ULTRACET/ ULTRACET SEMI is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol (acetaminophen) 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 (acetaminophen) overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Serious potential consequences of overdosage of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. In addition, cases of QT prolongation have been reported during overdose.

Paracetamol (Acetaminophen)

Paracetamol (Acetaminophen) in massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic overdosage may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment

A single or multiple overdose with ULTRACET/ ULTRACET SEMI may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol, 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.

In treating an overdosage of ULTRACET/ ULTRACET SEMI, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of an overdose. Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo- tracheal tube should be inserted when necessary, to provide assisted respiration.

In adult and pediatric patients, any individual presenting with an unknown amount of paracetamol

(acetaminophen) ingested or with a questionable or unreliable history about the time of ingestion should have a plasma paracetamol (acetaminophen) level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated paracetamol (acetaminophen) ingestion exceeds 7.5 to 10 grams for adults and adolescents or 150 mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

PHARMACOLOGICAL PROPERTIES

Chemical names

Tramadol hydrochloride

(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

Paracetamol (Acetaminophen)

N-acetyl-p-aminophenol (4-hydroxyacetanilide).

Pharmacodynamic Properties

Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics, ATC code: N02AJ13

Pharmacodynamic effects

Tramadol is a centrally acting analgesic compound. At least two complementary mechanisms appear applicable, binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Paracetamol (Acetaminophen) is another centrally acting analgesic. The exact site and mechanism of its analgesic action is not clearly defined.

When evaluated in a standard animal model, the combination of tramadol and paracetamol (acetaminophen) exhibited a synergistic effect.

Pharmacokinetic Properties

General

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and paracetamol (acetaminophen) following oral administration of one ULTRACET/ ULTRACET SEMI tablet are shown in Table 7. Tramadol has a slower absorption and longer half-life when compared to paracetamol (acetaminophen).

After a single oral dose of one Tramadol / Paracetamol (Acetaminophen) combination tablet (37.5 mg/325 mg) peak plasma concentrations of 64.3/55.5 ng/mL [(+)-Tramadol/(-)-Tramadol] and 4.2

µg/mL (paracetamol (acetaminophen)) are reached after 1.8 h [(+)-Tramadol/(-)-Tramadol] and 0.9 h (paracetamol / acetaminophen), respectively. Mean elimination half lives t1/2 are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (paracetamol (acetaminophen)).

Single and multiple dose pharmacokinetic studies of ULTRACET/ ULTRACET SEMI in volunteers showed no significant drug interactions between tramadol and paracetamol (acetaminophen).

Table 7: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Paracetamol (Acetaminophen) Following A Single Oral Dose of One Tramadol/ Paracetamol (Acetaminophen) Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		Paracetamol(Acetaminophen)	
Cmax	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
tmax (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)
t1/2 (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

[a] For paracetamol (acetaminophen), Cmax was measured as mcg/mL.

Absorption

Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two ULTRACET/ ULTRACET SEMI tablets occurs at approximately two and three hours, respectively, post-dose in healthy adults.

Oral absorption of paracetamol (acetaminophen) following administration of ULTRACET/ ULTRACET SEMI is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of paracetamol (acetaminophen) occur within 1 hour and are not affected by co-administration with tramadol.

Food effects

The oral administration of ULTRACET/ ULTRACET SEMI with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol (acetaminophen), so that ULTRACET/ ULTRACET SEMI can be taken independently of meal times.

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%.

Paracetamol (Acetaminophen) 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 (acetaminophen) is bound to plasma protein.

Metabolism

Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of ULTRACET/ ULTRACET SEMI in volunteers showed no significant change compared to dosing with tramadol alone.

Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. Tramadol is extensively metabolized by a number of pathways, including CYP2D6. Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients (see *Warnings and Precautions - CYP2D6 Ultra-Rapid Metabolism of Tramadol*). The prevalence of this CYP2D6 genotype varies by population and has been reported in literature to range from 1% to 10% in African Americans, Caucasian Americans, Asians and Europeans (including specific studies in Greeks, Hungarians and Northern Europeans) to as high as 29% in African/Ethiopians.

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

a) conjugation with glucuronide;
b) conjugation with sulfate; and
c) oxidation via cytochrome P450 enzyme pathway.

Excretion

Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of racemic tramadol and M1 are approximately six and seven hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing of ULTRACET/ ULTRACET SEMI.

The half-life of paracetamol (acetaminophen) is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Paracetamol (Acetaminophen) is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of paracetamol (acetaminophen) is excreted unchanged in the urine.

NON-CLINICAL INFORMATION

Tramadol / Paracetamol (Acetaminophen) Combination

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

No drug-related teratogenic effects were observed in the progeny of rats treated orally with the combination of tramadol and paracetamol (acetaminophen). The tramadol / paracetamol (acetaminophen) combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose (50/434 mg/kg tramadol / paracetamol (acetaminophen)) 8.3 times the maximum human dose but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. Lower and less severe maternally toxic dosages (10/87 and 25/217 mg/kg tramadol / paracetamol (acetaminophen)) did not produce embryo or fetal toxicity.

Tramadol Hydrochloride

Carcinogenicity and mutagenicity

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice (dosing orally up to 30 mg/kg 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 such finding occurred in a rat carcinogenicity study.

Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters.

Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

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.

Effect on reproduction

Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (6 to 10 times the maximum human dose). No toxicity was observed for progeny of dams receiving 8, 10, 20, 25 or 40 mg/kg. Maternal toxicity was observed at all dose levels of tramadol in this study, but effects on progeny were evident only at higher dose levels where maternal toxicity was more severe.

PHARMACEUTICAL INFORMATION

List of Excipients

Powdered Cellulose USNF, Pregalatinised Starch IP, Starch IP, Sodium Starch Glycolate IP (Plus), Magnesium Stearate IP, ** Purified Water IP (** Does not appear in final product), Colorant – Yellow Oxide of Iron, Titanium Dioxide IP.

Incompatibilities

None known

Shelf Life

See Mfg. date / Exp. Date printed on pack.

Storage Conditions

Store at a temperature not exceeding 30°C, protected from light.

Keep out of the sight & reach of children.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store ULTRACET/ULTRACET SEMI securely, in a location not accessible by others.

Warning: Taking more than the recommended daily dose, may cause serious liver damage or allergic reactions (e.g. swelling of the face, mouth and throat, difficulty in breathing, itching or rash).

In case of overdose, get medical help right away. Quick medical attention is critical even if you do not notice any signs or symptoms.

Instructions for Use and Handling and Disposal

Any unused ULTRACET/ULTRACET SEMI should be disposed of in accordance with local requirements.

Made in India by:

Johnson & Johnson Pvt. Ltd.,
Gala No. 3, BULDG No. B-2 Citylink Warehousing Complex,
S.No. 120-121, Mumbai Nashik Highway, Village Vadpe,
Taluka – Bhiwandi -421302, Maharashtra**.**

Manufactured at:

Encore Healthcare Pvt. Ltd.,
Plot No. D-5, M.I.D.C, Industrial Area,
Paithan, Aurangabad – 431148.

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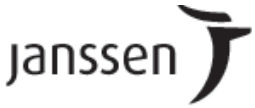
DATE OF REVISION OF THE TEXT

01 Jul 2024

Reference: Based on Company Core Data Sheet dated 30 Jan 2024.



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