NAME OF THE MEDICINAL PRODUCT
ULTRACET® (tramadol & paracetamol)

DOSAGE FORMS AND STRENGTHS
ULTRACET® tablets are available as light yellow, film-coated tablet. ULTRACET® tablets contain 37.5 mg of tramadol hydrochloride and 325mg of paracetamol. For excipients, see *List of Excipients.*

CLINICAL INFORMATION
Indications
ULTRACET® is indicated for the treatment of moderate to severe pain.

Dosage and Administration
The tablets should be taken orally, whole, not divided or chewed, with sufficient liquid, without regard to food. ULTRACET® should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with ULTRACET® is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Dosage - Adults and children 16 years of age and over
The maximum single dose of ULTRACET® is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

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

Children below 16 years of age
The use of ULTRACET® is contraindicated in children below 12 years of age (see *Contraindications*).

The safety and effectiveness of ULTRACET® 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*). Therefore, treatment is not recommended in this population.

Elderly (75 years of age and older)
Elimination of the active components may be prolonged in elderly patients over 75 years of age. Therefore, if necessary the dosage interval may be extended according to the patients requirements.

Renal Insufficiency/Dialysis/Hepatic Insufficiency
The pharmacokinetics of the tramadol/paracetamol combination in patients with renal impairment has not been studied. Experience with tramadol suggests that impaired renal function results in a decreased rate and extent of excretion of tramadol. In patients with creatinine clearances of less than 30mL/min, it is recommended that the dosing interval of ULTRACET® be increased not to exceed 2 tablets every 12 hours. The pharmacokinetics and

tolerability of ULTRACET® in patients with impaired hepatic function has not been studied. Tramadol and paracetamol are both extensively metabolized by the liver. The use of ULTRACET® in patients with severe hepatic impairment is not recommended.

Contraindications

ULTRACET® 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 or any other components (see *List of Excipients*) of this product or opioids.
- in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.
- in patients using monoamine oxidase inhibitors (MAOI) concurrently or within the last 14 days. (see *Interactions*)
- 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 anoretics), tricyclic antidepressants (TCAs) and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc), or opioids. Patients with epilepsy or those susceptible to seizures should only be treated with ULTRACET® if there are compelling circumstances.

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®.

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® 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, Metabolism*). 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® 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®) with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression.
ULTRACET® 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® should be used with caution patients with increased intracranial pressure or head injury.

Drug dependence and potential for abuse

ULTRACET® contains tramadol as an active ingredient. A portion of the analgesic effect of ULTRACET® 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® and monitor all patients receiving ULTRACET® 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® may reduce psychic and physical dependence of the morphine-type (mopioid).

ULTRACET® 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. Tramadol is not suitable as a substitute in opioid-dependent patient. Although it is an opioid agonist, it cannot suppress morphine withdrawal symptoms. Dependence and abuse, including drug-seeking behaviours and taking illicit actions to obtain this drug are not limited to those patients with poor history of opioid dependence. In severe respiratory insufficiency, ULTRACET® is not recommended.

Increased risk of hepatotoxicity with alcohol use

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

Treatment withdrawal

Withdrawal symptoms may occur if ULTRACET® 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® with great caution in patients taking serotonergic drugs including SSRIs. Concomitant use of tramadol with serotonergic drugs including SSRIs increases the risk of adverse events including seizure and serotonin syndrome (see *Interactions*).

Renal impairment

ULTRACET® 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® be increased not exceed 2 tablets every 12 hours.

Hepatic impairment
The use of ULTRACET® 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. 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®, 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® and appropriate treatment (e.g., fluid restriction). During ULTRACET® treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

Precautions general
The recommended dose of ULTRACET® should not be exceeded.

ULTRACET® should not be co-administered with other tramadol or paracetamol-containing compounds.

Interactions
Based on its pharmacodynamic and pharmacokinetic properties, tramadol and paracetamol 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 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®

Inhibitors of CYP2D6	
Mechanism:	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical Impact:	The concomitant use of ULTRACET® 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® 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 ultrarapid metabolism of tramadol*). If an inhibitor of CYP2D6 is discontinued, consider lowering ULTRACET® 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® 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® 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® is achieved. If an inhibitor of CYP3A4 is discontinued, consider increasing the ULTRACET® 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® 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® dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If an inducer of CYP3A4 is discontinued, consider ULTRACET® 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® 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® 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® in patients taking serotonergic drugs and monitor for signs of adverse events. Discontinue ULTRACET® 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® 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 with serotonergic drugs)* or opioid toxicity (e.g., respiratory depression, coma) (see *Warnings and Precautions – Respiratory depression*).
Intervention:	Do not use ULTRACET® 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® 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 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 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 acetaminophen as concurrent intake has been associated with HAGMA, especially in patients with risk factors. Discontinue ULTRACET® 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.
Opioid Agonists/ Antagonists	

Clinical Impact:	Concomitant administration of ULTRACET® and opioid agonist/antagonists (e.g., buprenorphine, nalbuphine, pentazocine) is not advisable, because the decreased analgesic effect by competitive blocking effect at the receptors can precipitate withdrawal syndrome.
Digoxin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.
Diflunisal	
Clinical Impact:	Concomitant use of diflunisal and paracetamol produces 50% increase in paracetamol plasma levels in normal volunteers. The clinical significance of these findings have not been established. ULTRACET® should be used cautiously and patients be monitored carefully.

Pregnancy and Breast-feeding

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or post-natal development (see *Preclinical Safety Data*). Tramadol has been shown to cross the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore ULTRACET® should not be used in pregnant women. The effect of ULTRACET® if any, on the later growth, development, and functional maturation of the child is unknown.

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

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

ULTRACET® 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® 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®.

Fertility

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

Effects on Ability to Drive and Use Machines

Even when used according to instructions, ULTRACET® 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 based on a comprehensive assessment of the available adverse event information. A causal relationship with tramadol hydrochloride/paracetamol 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® 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® 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™-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®-treated Patients and With an Incidence Greater Than Placebo in 16 Double-blind, Placebo-controlled Clinical Trials of ULTRACET®

	ULTRACET® % (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®-treated patients

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

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

System Organ Class Adverse Reaction	**ULTRACET®** **%** **(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®-treated patients

Adverse reactions not reported above, which were reported by <1% of ULTRACET®-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®-treated Patients in 21 Clinical Trials of ULTRACET®

System Organ Class Adverse Reaction	ULTRACET® % (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	

System Organ Class Adverse Reaction	ULTRACET® % (N=3,175)
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
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®-treated patients in the ULTRACET® 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® 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® is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both. The initial symptoms of tramadol overdose may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following a paracetamol overdose 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.

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

Paracetamol 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 overdoses with ULTRACET® may be a potentially lethal polydrug overdose, and immediate consultation with a regional poison control center or transfer to a hospital 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. Naloxone is not recommended in treating convulsions, since tramadol-induced convulsions were adversely affected by naloxone in animal experiments. In such cases diazepam should be given intravenously. Hemodialysis or hemofiltration is not expected to be helpful in an overdose because it removes less than 7% of the administered tramadol dose in a 4-hour dialysis period.

In treating an overdosage of ULTRACET®, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Keep open the respiratory tract (aspiration!); maintain respiration and circulation depending on the symptoms. 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 adults and adolescents, hepatic toxicity may occur following ingestion of 7.5 – 10 grams in a period of eight hours or less. Regardless of the quantity of paracetamol reported to have been ingested, the paracetamol antidote n-acetylcysteine should be administered orally or intravenously as soon as possible, if possible within 10 hours after intoxication. Plasma samples to determine paracetamol plasma levels should be taken but results of assays should not be awaited before initiating treatment with n-acetylcysteine.

Pharmacological Properties

Pharmacodynamic properties

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

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at opioid receptors with a higher affinity for the μ receptor. In addition, 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.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is not affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 10% - 17% that of morphine. Paracetamol is another centrally acting analgesic. Although the exact site and mechanism of its analgesic action is not clearly defined, paracetamol appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptor including N-methyl-D-aspartate and Substance P.

When evaluated in a standard animal model, the combination of tramadol and paracetamol exhibited a synergistic effect. That is, when tramadol and paracetamol were administered together, significantly less of each drug was needed to produce a given analgesic effect than would be expected if their effects were merely additive. Tramadol reaches peak activity in 2 to 3 hours with a prolonged analgesic effect, so that it’s combination with paracetamol, a rapid-onset, short-acting analgesic agent, provides substantial benefit to patients over either component alone.

Pharmacokinetic properties

General

Tramadol is administered as a racemate and both the [+] and [-] forms of both tramadol and its M1 metabolite are detected in the circulation. Although tramadol is rapidly absorbed after

administration, it has a slower absorption (and longer half-life), when compared to paracetamol.

After a single oral dose of one Tramadol/Paracetamol 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) are reached after 1.8h [(+)-Tramadol/(-)-Tramadol] and 0.9h (Paracetamol), respectively. Mean elimination half lives $t^1/_2$ are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (Paracetamol).

Single and multiple oral dose pharmacokinetic studies of ULTRACET® in volunteers showed no significant drug interactions between tramadol and paracetamol.

Absorption
Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100mg oral dose is approximately 75%. With multiple dosing, bioavailability increases to approximately 90%.

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

Food Effects
When ULTRACET® 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 concentration or the extent of absorption of either tramadol or paracetamol were not affected. The clinical significance of this difference is unknown.

Metabolism
Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of ULTRACET® in volunteers showed no significant change compared to dosing with tramadol alone. Tramadol is extensively metabolized after oral administration.
Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. 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 is primarily metabolized in the liver by first-order kinetics and involves as principal separate pathways:
- conjugation with glucuronide;
- conjugation with sulfate; and
- oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway.

Elimination
Tramadol and its metabolites are eliminated primarily by the kidney.

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

NON-CLINICAL INFORMATION

Preclinical Safety Data

Tramadol/Paracetamol Combination

There are no animal or laboratory studies on the combination product (tramadol and paracetamol) 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. 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) 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) did not produce embryo or fetal toxicity.

Carcinogenicity/Mutagenicity

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study with tramadol, 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.
Various animal bioassays on a weight-of-evidence basis have demonstrated no evidence of carcinogenic potential for paracetamol.

Tramadol was not mutagenic in the following assays: Ames Salmonella miscrosomal 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.
Paracetamol has been found to have no mutagenic potential using the Ames Salmonella – Microsomal Activation Test, the Basic test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Impairment of Fertility/Effect on Reproduction

No effects on fertility were observed for tramadol at oral dose levels up to 50mg/kg in male rats and 75mg/kg in female rats.

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

There was no effect on pregnancy or offspring when paracetamol alone was given at dose levels of 600 mg/kg/day in the diet of male rats for 60 days prior to mating and to female rats from 14 days before mating to the end of pregnancy. An oral dose of 600mg/kg/day produced no teratogenicity or embryotoxicity when given from days 6 through 15 of pregnancy. When paracetamol was given from day 16 of pregnancy through a 3-week lactation period, no deleterious effect was noted on pregnancy rate or on percent of live births, but a decrease in body weight gain and survival rate was noted among offspring of drug-treated females. In another study, paracetamol 250mg/kg/day did not affect fetal length or weight, incidence of resorptions, or placental weight.

PHARMACEUTICAL INFORMATION

List of excipients

Carnauba wax
Hypromellose
Iron oxide
Magnesium stearate
Maize starch
Polyethylene glycol
Polysorbate 80
Powdered cellulose
Pregelatinized starch
Sodium starch glycolate
Titanium dioxide

Incompatibilities

Not applicable.

Shelf-Life

Observe expiry date on outer pack

Storage Conditions

Store at room temperature not above 25˚C in the original package.
Keep out of reach of children.

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

Nature and Contents of Container

ULTRACET® tablets are packaged in blisters of standard PVC with aluminium foil backing, polypropylene with aluminium foil backing and polypropylene with polypropylene backing. Each blister contains one tablet. Packs sizes available are 2, 10, and multiples of 10 up to 60 tablets per pack (however, not all pack sizes listed may be marketed).

Instructions for Use and Handling and Disposal

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

Product Registrant

Johnson & Johnson Pte Ltd
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

Batch Releaser

Janssen-Cilag S.p.A.
Via C. Janssen (loc. Borgo S. Michele)
04100 Latina (LT), Italy

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