janssen

NAME OF THE MEDICINAL PRODUCT
Tradenames
ULTRACET®

International Non-Proprietary Names
Tramadol
Acetaminophen

QUALITATIVE AND QUANTITATIVE COMPOSITION
ULTRACET® is available as tablets for oral administration containing 37.5 mg tramadol hydrochloride and 325 mg acetaminophen (N-acetyl-p-aminophenol)

PHARMACOLOGICAL PROPERTIES
Chemical Names
Tramadol Hydrochloride
(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

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 synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, 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.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see Pharmacokinetics).

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.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.

Acetaminophen
Acetaminophen is a non-opiate, non-salicylate analgesic.

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 acetaminophen following oral administration of one ULTRACET® tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Table 1. Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

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

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

A single dose pharmacokinetic study of ULTRACET® in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite m1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-m1 and 24.2% for (-)-m1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of Ultracet®, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

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

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Oral absorption of acetaminophen following administration of ULTRACET® occurs primarily in the small intestine.

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 acetaminophen. However, peak plasma concentration or the extent of absorption of either tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.

Distribution
The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range. Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism
Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites.

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. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see Precautions, drug interactions).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as Fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see warnings) and serotonin syndrome.

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, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP2A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of ULTRACET®. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of Ultracet®. The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations
Renal
The pharmacokinetics of ULTRACET® in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min, adjustment of dosing regimen in this patient population is recommended. (See dosage and administration). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic
The pharmacokinetics and tolerability of ULTRACET® in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of ULTRACET® in patients with hepatic impairment is not recommended (see precautions and dosage and administration).

Geriatric
A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with ULTRACET® which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function (see precautions, geriatric use).

Gender
Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of ULTRACET® in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

Pediatric
Pharmacokinetics of ULTRACET® tablets have not been studied in pediatric patients below 16 years of age.

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

INDICATIONS
ULTRACET® is indicated for short-term treatment of acute pain.

POSOLOGY AND METHOD OF ADMINISTRATION
Unless otherwise prescribed, ULTRACET® should be administered as follows:

Adults and Children Over 16 Years
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.

ULTRACET® can be administered without regard to food.

Treatment withdrawal

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

Pediatric (Children Below 16 Years)
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 Special Warnings and Special Precaution for Use - Other Risk Factors for Life-threatening Respiratory Depression in Children*).

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

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
WARNINGS
Seizures Risk
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, 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® (see contraindications).
Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome.

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. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see warnings, seizure risk and Overdosage).

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 *Posology and Method of 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® 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 *Posology and Method of Administration and Overdose - Symptoms and signs, Tramadol*).

Interaction 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. Tramadol increases the risk of CNS and respiratory depression in these patients. (see Interaction)

Increased Intracranial Pressure or Head Trauma
ULTRACET® should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients.

Additionally, papillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRACET® (see Respiratory Depression).

Use in Ambulatory Patients
Tramadol may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Use with serotonergic drugs
Use ULTRACET® 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*).

Increase risk of Hepatotoxicity with alcohol use
ULTRACET® should not be used concomitantly with alcohol consumption. The use of Ultracet® in patients with liver disease is not recommended.

Use with Other Acetaminophen-containing Products
Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, ULTRACET® should not be used concomitantly with other acetaminophen-containing products.

Withdrawal
Withdrawal symptoms may occur if ULTRACET® is discontinued abruptly. (see drug abuse and dependence). These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with ULTRACET® discontinuation include: panic attacks, severe anxiety and paresthesias, tinnitus and unusual CNS symptoms. Clinical experience suggests that withdrawal symptoms may be avoided by tapering ULTRACET® at the time of discontinuation.

Physical Dependence and 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).
Tramadol may induce physic and physical dependence of the morphine-type (μ-opioid). (see Drug Abuse and Dependence). Tramadol 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. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence.

Risk of Overdosage
Serious potential consequences of Overdosage with tramadol are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. (see Overdosage).

Serious potential consequences of overdosage with acetaminophen are hepatic (centrilobular) necrosis, leading to hepatic failure and death. Emergency help should be sought immediately and treatment initiated immediately if overdose is suspected, even if symptoms are not apparent.

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.
Do not co-administer ULTRACET® with other tramadol or acetaminophen-containing products. (see Warnings, use with other acetaminophen-containing products and risk of Overdosage).

Pediatric Use
The safety and effectiveness of ULTRACET® has not been studied in the pediatric population.

Geriatric Use
In general, dose selection for an elderly patient should be cautions, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease and multiple drug therapy.

Acute Abdominal Conditions
The administration of ULTRACET® may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal Disease
ULTRACET® has not been studied in patients with impaired renal function. Experience with tramadol suggest that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET® be increased not to exceed 2 tablets every 12 hours.

Use in Hepatic Disease
ULTRACET® has not been studied in patients with impaired hepatic function. The use of ULTRACET® in patients with hepatic impairment is not recommended (see warnings, use with alcohol).

Information for Patients
- ULTRACET® may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- ULTRACET® should not be taken with alcohol containing beverages.
- The patient should be instructed not to take ULTRACET® in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations.

- ULTRACET® should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see precautions, labor and delivery).
- The patients should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, hepatic toxicity and death.

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, acetaminophen, any other component of this product or opioids.
- in any situation where opioids are contraindicated, including acute intoxication without of the following 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 *Special Warnings and Special Precaution for Use*).

UNDESIRABLE EFFECTS

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/acetaminophen based on a comprehensive assessment of the available adverse event information. A causal relationship with tramadol hydrochloride/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® 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**Error! Reference source not found.**. 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 dreamsa	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

System Organ Class Adverse Reaction
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	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000
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

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Based on its pharmacodynamic and pharmacokinetic properties, tramadol and 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 acetaminophen be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Table 7. 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 *Special Warnings and Special Precaution for Use – CYP2D6 ultra rapid 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 *Special Warnings and Special Precaution for Use*).
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 *Special Warnings and Special Precaution for Use – use with serotonin reuptake inhibitors)* or opioid toxicity (e.g., respiratory depression, coma) (see *Special Warnings and Special Precaution for Use –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 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.
Cimetidine	
Clinical Impact:	Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

PREGNANCY AND BREAST-FEEDING

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®, 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® 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®.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

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, acetaminophen toxicity or both. The initial symptoms seen within the first 24 hours following an 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.

Acetaminophen

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® 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®, 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 acetaminophen ingested or with a questionable or unreliable history about the time of ingestion should have a plasma acetaminophen level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, OPADRY® Light Yellow, and carnauba wax.

Incompatibilities

None known

Shelf Life

3 years

Special Precautions for Storage

Do not store above 30°C. Store 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.

HOW SUPPLIED

ULTRACET® Tablet
Box @ 3 blister @ 10 tablets
Reg. No.: DKI1910901510A1

HARUS DENGAN RESEP DOKTER

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