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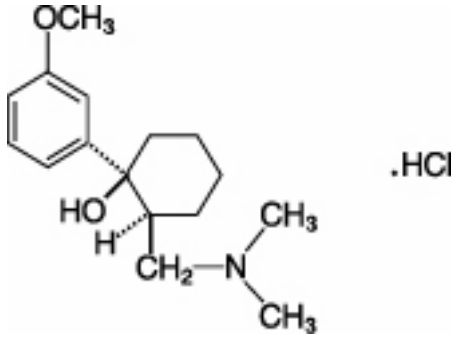
ULTRAM® (tramadol hydrochloride tablets)

DESCRIPTION

ULTRAM® (tramadol hydrochloride tablets) is a centrally acting analgesic. The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. ULTRAM tablets contain 50 mg of tramadol hydrochloride and are white in color. Inactive ingredients in the tablet are corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax.

CLINICAL PHARMACOLOGY

Pharmacodynamics

ULTRAM 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 CLINICAL PHARMACOLOGY, 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 ULTRAM. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

Apart from analgesia, ULTRAM administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, ULTRAM has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacokinetics

The analgesic activity of ULTRAM is due to both parent drug and the M1 metabolite (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Tramadol is administered as a racemate and both the [-] and

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[+] forms of both tramadol and M1 are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. Tramadol has a volume of distribution of approximately 2.7L/kg and is only 20% bound to plasma proteins. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. The formation of M1 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS, Drug Interactions). Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption:
Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~ 10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with q.i.d. dosing. There is no evidence of self-induction (see Figure 1 and Table 1 below).

Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given q.i.d.

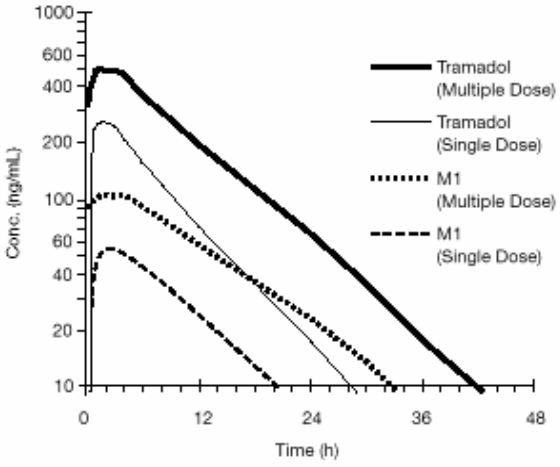

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Table 1
Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/ Dosage Regimen[a]	Parent Drug/ Metabolite	Peak Conc. (ng/mL)	Time to Peak (hrs)	Clearance/F[b] (mL/min/Kg)	$t_{1/2}$ (hrs)
Healthy Adults, 100 mg qid, MD p.o.	Tramadol	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
	M1	110 (29)	2.4 (46)	c	7.0 (14)
Healthy Adults, 100 mg SD p.o.	Tramadol	308 (25)	1.6 (63)	8.50 (31)	5.6 (20)
	M1	55.0 (36)	3.0 (51)	c	6.7 (16)
Geriatric, (>75 yrs) 50 mg SD p.o.	Tramadol	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
	M1	d	d	c	d
Hepatic Impaired, 50 mg SD p.o.	Tramadol	217 (11)	1.9 (16)	4.23 (56)	13.3 (11)
	M1	19.4 (12)	9.8 (20)	c	18.5 (15)
Renal Impaired, CL_{cr}10-30 mL/min 100 mg SD i.v.	Tramadol	c	c	4.23 (54)	10.6 (31)
	M1	c	c	c	11.5 (40)
Renal Impaired, CL_{cr}<5 mL/min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)	11.0 (29)
	M1	c	c	c	16.9 (18)

a SD = Single dose, MD = Multiple dose, p.o.= Oral administration, i.v.= Intravenous administration, q.i.d. = Four times daily
b F represents the oral bioavailability of tramadol
c Not applicable
d Not measured

Food Effects: Oral administration of ULTRAM with food does not significantly affect its rate or extent of absorption, therefore, ULTRAM can be administered without regard to food.

Distribution:
The volume of distribution of tramadol was 2.6 and 2.9 liters/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.

Metabolism:
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. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. One metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS, Drug Interaction).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of

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

Elimination:
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing.

Special Populations

Renal:
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, adjustment of the dosing regimen 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.

Hepatic:
Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION).

Geriatric:
Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see DOSAGE AND ADMINISTRATION).

Gender:
The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

Clinical Studies

ULTRAM has been given in single oral doses of 50, 75 and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).

In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg ULTRAM tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.

ULTRAM has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving ULTRAM. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of ULTRAM in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL® with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX®) daily.

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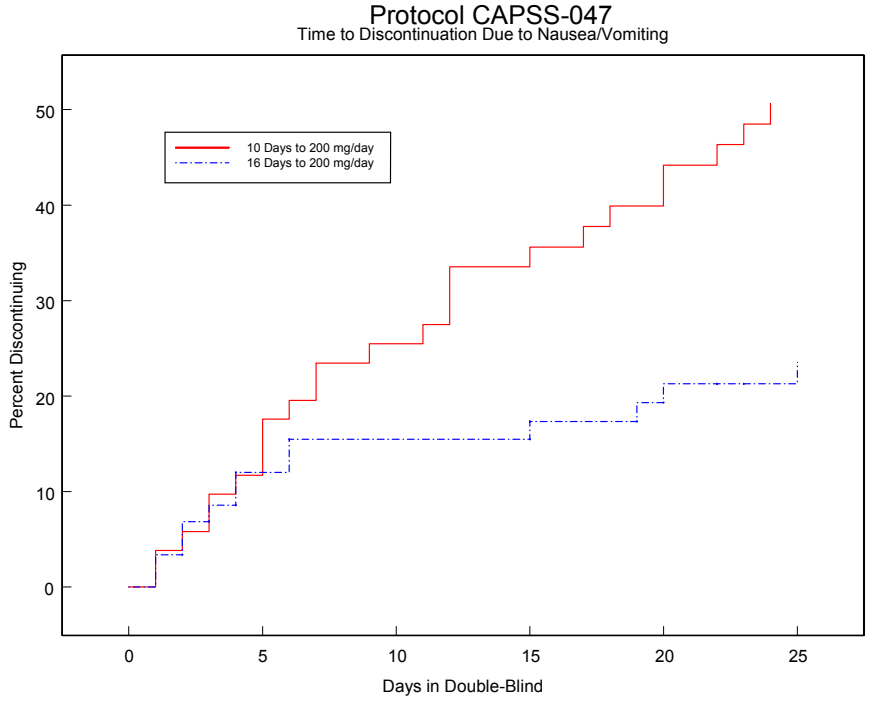
Titration Trials

In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate ULTRAM therapy using slower titration rates.

A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule.

Figure 2:



INDICATIONS AND USAGE

ULTRAM is indicated for the management of moderate to moderately severe pain in adults.

CONTRAINDICATIONS

ULTRAM should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. ULTRAM is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRAM may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving ULTRAM within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of ULTRAM

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above the recommended range. Concomitant use of ULTRAM increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of ULTRAM may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors),**
- **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 ULTRAM overdose, naloxone administration may increase the risk of seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with ULTRAM. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRAM (see CONTRAINDICATIONS).

Respiratory Depression

Administer ULTRAM cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of ULTRAM 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).

Interaction With Central Nervous System (CNS) Depressants

ULTRAM should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. ULTRAM increases the risk of CNS and respiratory depression in these patients.

Increased Intracranial Pressure or Head Trauma

ULTRAM 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, pupillary 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 ULTRAM. (See Respiratory Depression.)

Use in Ambulatory Patients

ULTRAM 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.

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Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors

Use ULTRAM with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of ULTRAM with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Withdrawal

Withdrawal symptoms may occur if ULTRAM 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 ULTRAM discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering ULTRAM at the time of discontinuation.

Physical Dependence and Abuse

ULTRAM may induce psychic and physical dependence of the morphine-type (μ-opioid) (see DRUG ABUSE AND DEPENDENCE). ULTRAM should not be used in opioid-dependent patients. ULTRAM 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 ULTRAM (tramadol hydrochloride tablets) 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).

PRECAUTIONS

Acute Abdominal Conditions

The administration of ULTRAM may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal and Hepatic Disease

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, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION).
With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

Information for Patients

- ULTRAM may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- ULTRAM should not be taken with alcohol containing beverages.
- ULTRAM 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 patient 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 and death.

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Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Use With Carbamazepine
Patients taking **carbamazepine** may have a significantly reduced analgesic effect of ULTRAM. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of ULTRAM and carbamazepine is not recommended.

Use With Quinidine
Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and ULTRAM results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use With Inhibitors of CYP2D6
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use With Cimetidine
Concomitant administration of ULTRAM with **cimetidine** does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRAM dosage regimen is recommended.

Use With MAO Inhibitors
Interactions with **MAO Inhibitors**, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use With MAO Inhibitors).

Use With Digoxin and Warfarin
Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.36 times the maximum daily human dosage of 246 mg/m^2) 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 (dosing orally up to 30 mg/kg, 180 mg/m^2, or 0.73 times the maximum daily human dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

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No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m^2, respectively.

Pregnancy, Teratogenic Effects: *Pregnancy Category C*

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m^2), rats (≥25 mg/kg or 150 mg/m^2) and rabbits (≥75 mg/kg or 900 mg/m^2) at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages on a mg/m^2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m^2) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m^2), rats (up to 80 mg/kg or 480 mg/m^2) or rabbits (up to 300 mg/kg or 3600 mg/m^2) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m^2), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m^2), respectively.

Non-teratogenic Effects
Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/ m^2 or 1.2 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 1.9 and higher the maximum daily human dose).

There are no adequate and well-controlled studies in pregnant women. ULTRAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

Labor and Delivery

ULTRAM should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see DRUG ABUSE AND DEPENDENCE). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRAM, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours postdose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

Pediatric Use

The safety and efficacy of ULTRAM in patients under 16 years of age have not been established. The use of ULTRAM in the pediatric population is not recommended.

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Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

A total of 455 elderly (65 years of age or older) subjects were exposed to ULTRAM in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

ADVERSE REACTIONS

ULTRAM was administered to 550 patients during the double-blind or open-label extension periods in U.S. studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 2 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to ULTRAM administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for ULTRAM and the active control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the ULTRAM groups.

Table 2: Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain (N=427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"[1]	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

[1] "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Incidence 1% to less than 5%, possibly causally related: the following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists.

Body as a Whole: Malaise.

Cardiovascular: Vasodilation.

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Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.

Gastrointestinal: Abdominal pain, Anorexia, Flatulence.

Musculoskeletal: Hypertonia.

Skin: Rash.

Special Senses: Visual disturbance.

Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Incidence less than 1%, possibly causally related: the following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in post-marketing experience.

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).

Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.

Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see WARNINGS), Tremor.

Respiratory: Dyspnea.

Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.

Special Senses: Dysgeusia.

Urogenital: Dysuria, Menstrual disorder.

Other adverse experiences, causal relationship unknown: A variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials and/or reported in post-marketing experience. A causal relationship between ULTRAM and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.

Central Nervous System: Migraine, Speech disorders.

Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.

Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.

Sensory: Cataracts, Deafness, Tinnitus.

DRUG ABUSE AND DEPENDENCE

ULTRAM may induce psychic and physical dependence of the morphine-type (μ-opioid). (See WARNINGS.) 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. The risk in patients with substance abuse has been observed to be higher. ULTRAM is associated with craving and tolerance development. Withdrawal symptoms may occur if ULTRAM is discontinued abruptly. 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 ULTRAM discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical

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experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS.) Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with ULTRAM. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with ULTRAM, the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

DOSAGE AND ADMINISTRATION

Adults (17 years of age and over)
For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**
For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day**.

Individualization of Dose

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

- In all patients with **creatinine clearance less than 30 mL/min,** it is recommended that the dosing interval of ULTRAM be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.
- The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.
- In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years old**, total dose should not exceed 300 mg/day.

HOW SUPPLIED

ULTRAM (tramadol hydrochloride tablets) Tablets - 50 mg (white, scored, film-coated capsule-shaped tablet) debossed “ULTRAM” on one side and “06 59” on the other side.

100's NDC 0045-0659-60 bottles of 100 tablets

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500's NDC 0045-0659-70 bottles of 500 tablets

Packages of 100 unit doses in blister packs - NDC 0045-0659-10 (10 cards of 10 tablets each).

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F).

OMP DIVISION
ORTHO-McNEIL
PHARMACEUTICAL, INC.
Raritan, New Jersey 08869
U.S. Patents 3,652,589 and 3,830,934
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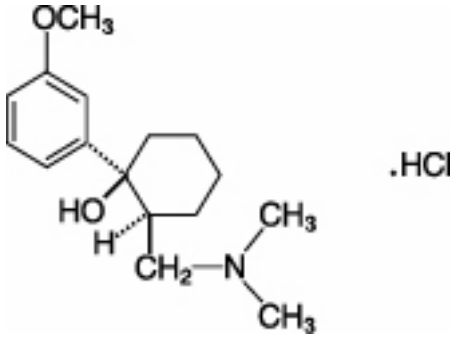
ULTRACET™ (tramadol hydrochloride/acetaminophen tablets)

DESCRIPTION

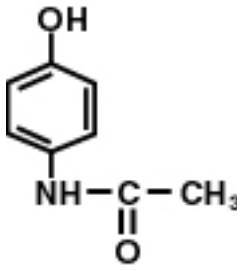
ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets) combines two analgesics, tramadol and acetaminophen.

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



The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol. It's structural formula is:



The molecular weight of acetaminophen is 151.17. Acetaminophen is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

ULTRACET Tablets contain 37.5 mg tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, OPADRY® Light Yellow, and carnauba wax.

CLINICAL PHARMACOLOGY

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

Pharmacodynamics

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

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the plasma concentrations of each compound (see CLINICAL PHARMACOLOGY, 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.

Pharmacokinetics

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 µg/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 absolute 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 ULTRAM® 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,

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

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

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.

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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 AND USAGE

ULTRACET is indicated for the short-term (five days or less) management of acute pain.

CONTRAINDICATIONS

ULTRACET should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids. ULTRACET is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRACET may worsen central nervous system and respiratory depression in these patients.

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WARNINGS

Seizure 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:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS – Use with MAO Inhibitors),**
- **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.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET (see CONTRAINDICATIONS).

Respiratory Depression

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).

Interaction With Central Nervous System (CNS) Depressants

ULTRACET should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients**.**

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.

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Additionally, pupillary 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 MAO Inhibitors and Serotonin Re-uptake Inhibitors

Use ULTRACET with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Use With Alcohol

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. Clinical experience suggests that withdrawal symptoms may be avoided by tapering ULTRACET at the time of discontinuation.

Physical Dependence and Abuse

Tramadol may induce psychic 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.

PRECAUTIONS

General

The recommended dose of ULTRACET should not be exceeded.

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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 cautious, 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 patient 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.

Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple

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oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Use With Carbamazepine
Patients taking **carbamazepine** 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.

Use With Quinidine
Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.
Use With Inhibitors of CYP2D6
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.
Use With Cimetidine
Concomitant administration of ULTRACET and **cimetidine** has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRACET dosage regimen is recommended.
Use With MAO Inhibitors
Interactions with **MAO Inhibitors**, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use with MAO Inhibitors).
Use With Digoxin
Post-marketing surveillance of tramadol has revealed rare reports of **digoxin** toxicity.
Use With Warfarin Like Compounds
Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.
While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when ULTRACET and warfarin-like compounds are administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.5 times the maximum daily human tramadol dosage of 185 mg/m^2) 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 rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 1 time the maximum daily human tramadol dosage).

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

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the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (350 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.6 and 2.4 times the maximum daily human tramadol dosage of 185 mg/m^2.

Pregnancy

Teratogenic Effects: *Pregnancy Category C*
No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m^2 or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m^2), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Non-teratogenic effects:

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 2.6 times the maximum daily human tramadol dosage).

There are no adequate and well-controlled studies in pregnant women. ULTRACET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported with tramadol hydrochloride during post-marketing.

Labor and Delivery

ULTRACET should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. (See DRUG ABUSE AND DEPENDENCE.) Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRACET, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRACET is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

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

ADVERSE REACTIONS

Table 2 reports the incidence rate of treatment-emergent adverse events over five days of ULTRACET use in clinical trials (subjects took an average of at least 6 tablets per day).

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

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

* Number of males = 62

Incidence at least 1%, causal relationship at least possible or greater: the following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of ULTRACET.

Body as a Whole – Asthenia, fatigue, hot flushes
Central and Peripheral Nervous System – Dizziness, headache, tremor
Gastrointestinal System – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting
Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence
Skin and Appendages – Pruritus, rash, increased sweating.

Selected Adverse events occurring at less than 1%: the following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in ULTRACET clinical trials.

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome
Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension
Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo
Gastrointestinal System – Dysphagia, melena, tongue edema
Hearing and Vestibular Disorders – Tinnitus
Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia
Liver and Biliary System – Hepatic function abnormal
Metabolic and Nutritional Disorders – Weight decrease
Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking
Red Blood Cell Disorders – Anemia
Respiratory System – Dyspnea
Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention
Vision Disorders – Abnormal vision
Other clinically significant adverse experiences previously reported with tramadol hydrochloride.
Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial

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ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

Other clinically significant adverse experiences previously reported with acetaminophen.
Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

DRUG ABUSE AND DEPENDENCE

Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid). (See WARNINGS.) Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with a prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. Tramadol is associated with craving and tolerance development. Withdrawal symptoms may occur if tramadol is discontinued abruptly. 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. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

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 of tramadol overdosage may include respiratory depression and or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS.) Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with tramadol.

Acetaminophen

Serious potential consequences of overdosage with acetaminophen are hepatic centrilobular necrosis, leading to hepatic failure and death. Renal tubular necrosis, hypoglycemia and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post ingestion.

Treatment of Overdose

A single or multiple overdose with ULTRACET may be a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

In treating an overdose of ULTRACET, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone

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administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. 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.

Standard recommendations should be followed for the treatment of acetaminophen overdose.

DOSAGE AND ADMINISTRATION

For the short-term (five days or less) management of acute pain, the recommended dose of ULTRACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Individualization of Dose

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. Dose selection for an elderly patient should be cautious, in view of the potential for greater sensitivity to adverse events.

HOW SUPPLIED

ULTRACET (37.5 mg tramadol hydrochloride/325 mg acetaminophen) Tablets (light yellow, film-coated capsule-shaped tablet) debossed “O-M” on one side and “650” on the other are available as follows:

20’s: NDC 0045 0650 50 (Bottles of 20 tablets)

100’s: NDC 0045 0650 60 (Bottles of 100 tablets)

500’s: NDC 0045 0650 70 (Bottles of 500 tablets)

HUD 100’s: NDC 0045 0650 10 (Packages of 100 unit doses in blister packs, 10 cards of 10 tablets each)

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 - 86°F).

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PHARMACEUTICAL, INC.
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