

PRODUCT MONOGRAPH

PrULTRAM^{®*}

tramadol hydrochloride Tablets, USP

50 mg

Opioid Analgesic

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Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

www.jansseninc.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	tablet 50 mg	carnauba wax, corn starch, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

INDICATIONS AND CLINICAL USE

Adults

ULTRAM[®] (tramadol hydrochloride) is indicated for the management of moderate to moderately severe pain in adults.

Geriatrics (> 65 years of age):

Healthy elderly subjects aged 65 to 75 years administered tramadol have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. ULTRAM[®] should be administered with greater caution in patients older than 75 years, due to the greater potential for adverse events in this population (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age):

The safety and effectiveness of ULTRAM[®] have not been studied in the pediatric population. Therefore, use of ULTRAM[®] tablets is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- ULTRAM[®] should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, opioids or to any component of this product.
- ULTRAM[®] is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRAM[®] may worsen central nervous system and respiratory depression in these patients.
- The concomitant use of ULTRAM[®] and MAO inhibitors (or within 14 days following discontinuation of such therapy) is contraindicated.

WARNINGS AND PRECAUTIONS

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

- selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics) (see **Use with Serotonin Reuptake Inhibitors**);
- 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 **CONTRAINDICATIONS**);
- 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 tramadol. When these rare reactions 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[®] tablets (see **CONTRAINDICATIONS**).

Drug Abuse, Addiction and Dependence

ULTRAM[®] has the potential to cause psychic and physical dependence of the morphine-type

(μ -opioid). The drug has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on ULTRAM[®] have been reported. ULTRAM[®] tablets should not be used in opioid-dependent patients. ULTRAM[®] can re-initiate physical dependence in patients who have been previously dependent or chronically using other opioids. In patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically using opioids, treatment with ULTRAM[®] is not recommended.

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

A Risk Management strategy to support the safe and effective use of ULTRAM[®] has been established. The following are considered to be the essential components of the Risk Management strategy:

- a) Commitment to not emphasize or highlight the scheduling status of ULTRAM[®] (i.e., not listed under a schedule to the CDSA) in its advertising or promotional activities.
- b) Inclusion of a PAAB-approved fair balance statement in all ULTRAM[®] advertising and promotional materials.
- c) Assurance that health-care education activities on pain management with ULTRAM[®] include balanced, evidence-based and current information. Commitment to take reasonable actions to inform health-care professionals that there is Health Canada-approved patient information on benefits and risks, and to ensure that this information can be readily accessed through electronic and/or hard copy sources.

ULTRAM[®] should not be used in opioid-dependent patients since it cannot suppress morphine withdrawal symptoms, even though it is an opioid agonist.

Abuse and addiction are separate and distinct from physical dependence and tolerance. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Tolerance as well as both physical and psychological dependence may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Withdrawal Symptoms

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 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.

Risk of Overdosage

Serious potential consequences of overdosage with ULTRAM[®] 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**).

Do not prescribe ULTRAM[®] for patients who are suicidal or addiction-prone.

ULTRAM[®] should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

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 ULTRAM[®] 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**, **Respiratory Depression**).

Respiratory

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 **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.

ULTRAM[®] may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Use with Alcohol

ULTRAM[®] should not be used concomitantly with alcohol consumption.

Use in Ambulatory Patients

ULTRAM[®] may impair mental 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

Concomitant use of ULTRAM[®] with MAO inhibitors is contraindicated (see **CONTRAINDICATIONS**).

Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of ULTRAM[®] with MAO inhibitors increases the risk of adverse events, including seizure (see **Seizure Risk** and **DRUG INTERACTIONS**) and serotonin syndrome.

Use with Serotonin Reuptake Inhibitors

Concomitant use of ULTRAM[®] with SSRIs increases the risk of adverse events, including seizure (see **Seizure Risk**) and serotonin syndrome. When co-administration of ULTRAM[®] and SSRIs is indicated, monitor the patient for seizures and possible early signs and symptoms of serotonin syndrome. Early symptoms of serotonin syndrome may include myoclonus, tremors, hyper-reflexia, diaphoresis, fever, tachycardia, tachypnoea, labile blood pressure, altered mental status (agitation, hallucinations, coma, excitement) and /or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Gastrointestinal

Acute Abdominal Conditions

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

Use in Drug and Alcohol Addiction

ULTRAM[®] is an opioid with no approved use in the management of addictive disorders.

Carcinogenesis and Mutagenesis

See *Product Monograph PART II, TOXICOLOGY*.

Special Populations

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, a dose 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, adjustment of the dosing regimen 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.

Pregnant Women:

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 stillbirth have been reported with tramadol hydrochloride during post-marketing.

ULTRAM[®] should not be used in pregnant women prior to or during labour 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 postpartum withdrawal symptoms in the newborn (see **Drug Abuse, Addiction 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 labour.

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

Nursing Women:

ULTRAM[®] is not recommended for obstetrical pre-operative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Following a single 100 mg i.v. 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.

Pediatrics (< 18 years of age):

The safety and effectiveness of ULTRAM[®] has not been studied in the pediatric population. Therefore, use of ULTRAM[®] tablets is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age):

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 **ACTION AND 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

Adverse Drug Reaction Overview

The most commonly reported adverse reactions are dizziness, nausea, constipation, headache, somnolence and vomiting as presented in Table 1.1.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Incidence of Adverse Reactions for ULTRAM[®] in Chronic Trials of Non-Malignant Pain - (non-titration trials)

ULTRAM[®] was administered to 550 patients during the double-blind or open-label extension periods in studies of chronic non-malignant pain. Of these patients, 375 were 65 years old or older. Table 1.1 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. The overall incidence rates of adverse experiences in these trials were similar for ULTRAM[®] and the active control groups, acetaminophen with codeine, and aspirin with codeine; however, the rates of withdrawals due to adverse events appeared to be higher in the ULTRAM[®] group. In the tramadol treatment groups, 16.8-24.5% of patients withdrew due to an AE, compared to 9.6-11.6% for acetaminophen with codeine and 18.5% for aspirin with codeine.

Table 1.1: Cumulative Incidence of Adverse Reactions for ULTRAM[®] in Chronic Trials of Non-Malignant Pain

	Percentage of Patients with Adverse Reaction		
	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” ^a	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

^a “CNS Stimulation” is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations

Two titration trials showed that the incidence of withdrawal due to AEs could be significantly reduced by using dose titration.

Incidence of Adverse Reactions for ULTRAM® CAPSS-047 Titration Trial

In the double-blind phase of this pivotal trial, gastrointestinal complaints (primarily nausea and vomiting) and dizziness were the adverse events reported most frequently by tramadol-treated subjects, Table 1.2. Most of the adverse events were assessed as mild or moderate in intensity and resolved.

Table 1.2 Adverse Events in CAPSS-047 - Double-Blind Phase - Frequently Reported ($\geq 2\%$ ^a) Adverse Events^b and Total Incidence of AEs Summarized by WHOART Body System, Treatment Group and Preferred Term

AEs in CAPSS-047 Double-Blind Phase $\geq 2\%$ of patients						
Tramadol Group/Titration Schedule						
Body System	10-days to 200 mg/day N = 54		16-days to 200 mg/day N = 59		13-days to 150 mg/day N = 54	
Preferred Term	n	%	n	%	n	%
Any Adverse Event	41	75.9	41	69.5	33	61.1
Body as a Whole – General Disorders						
Influenza-like symptoms	0	0.0	2	3.4	0	0.0
Pain	1	1.9	2	3.4	0	0.0
Fatigue	0	0.0	0	0.0	2	3.7
Central & Peripheral Nervous System Disorders						
Dizziness	4	7.4	4	6.8	4	7.4
Headache	10	18.5	9	15.3	7	13.0
Gastrointestinal System Disorders						
Mouth Dry	0	0.0	1	1.7	3	5.6
Constipation	4	7.4	2	3.4	6	11.1
Diarrhea	4	7.4	3	5.1	1	1.9
Vomiting	10	18.5	7	11.9	4	7.4
Nausea	29	53.7	25	42.4	18	33.3
Psychiatric Disorders						
Insomnia	1	1.9	2	3.4	2	3.7
Somnolence	5	9.3	4	6.8	0	0.0
Reproductive Disorders, Female						
Menstrual Disorder	0	0.0	2	2.0	0	0.0
Reproductive Disorders, Male						
Epididymitis	0	0.0	0	0.0	1	11.1
Respiratory Systems Disorders						
Coughing	0	0.0	3	5.1	0	0.0
Sinusitis	1	1.9	2	3.4	2	3.7
Upper Resp Tract Infection	2	3.7	0	0.0	0	0.0
Skin and Appendages Disorders						
Pruritis	2	3.7	1	1.7	4	7.4
Rash	0	0.0	2	3.4	2	3.7

^a Preferred terms reported by $\geq 2\%$ of subjects in one or more treatment groups, intent-to-treat population.

^b Number of patients with adverse event; numbers shown are all events regardless of relationship to study drug.

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.

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 AND PRECAUTIONS**), 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.

Other Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Tramadol Hydrochloride

Adverse events which have been reported with the use of tramadol products include: allergic reactions (including anaphylaxis, angioneurotic edema and urticaria), bradycardia, convulsions, drug dependence, drug withdrawal (including agitation, anxiety, gastrointestinal symptoms, hyperkinesia, insomnia, nervousness, tremors), hyperactivity, hypoactivity, hypotension and respiratory depression. Other adverse events which have been reported with the use of tramadol products and for which a causal association has not been determined include: difficulty

concentrating, hepatitis, liver failure, pulmonary edema, Stevens-Johnson syndrome and suicidal tendency.

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 SSRI's and MAOIs.

DRUG ABUSE, ADDICTION AND DEPENDENCE

Tramadol may induce psychic and physical dependence of the morphine-type (μ -opioid) (see **WARNINGS AND PRECAUTIONS, Drug Abuse, Addiction and Dependence**).

Dependence and abuse, including drug-seeking behaviour 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.

A Risk Management program to support the safe and effective use of ULTRAM[®] has been established. The following are considered to be the essential components of the Risk Management program:

- a) Commitment to not emphasize or highlight the scheduling status of ULTRAM[®] (i.e., not listed under a schedule to the CDSA) in its advertising or promotional activities.
- b) Inclusion of a PAAB-approved fair balance statement in all ULTRAM[®] advertising and promotional materials.
- c) Assurance that health-care education activities on pain management with ULTRAM[®] include balanced, evidence-based and current information. Commitment to take reasonable actions to inform health-care professionals that there is Health Canada-approved patient information on benefits and risks, and to ensure that this information can be readily accessed through electronic and/or hard copy sources.

Withdrawal Symptoms

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

DRUG INTERACTIONS

Overview

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.

Drug-Drug Interactions

Use with MAO Inhibitors

ULTRAM[®] is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**).

Drugs that Lower Seizure Threshold

Tramadol can increase the potential for selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions. If concomitant treatment of ULTRAM[®] with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS AND PRECAUTIONS, Use with Serotonin Reuptake Inhibitors**).

CNS Depressants

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, centrally acting analgesics, opioids and psychotropic drugs may potentiate CNS depressant effects (see **WARNINGS AND PRECAUTIONS**).

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 the CYP2D6 P450 isoenzyme. 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 CYP2D6 and CYP3A4 Inhibitors

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**), such as quinidine, fluoxetine, paroxetine, amitriptyline (CYP2D6 inhibitors), ketoconazole and erythromycin (CYP3A4

inhibitors), may reduce metabolic clearance of tramadol, increasing the risk for serious adverse events including seizures and serotonin syndrome.

Use with Cimetidine

Concomitant administration of ULTRAM[®] and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRAM[®] dosage regimen is recommended.

Use with Digoxin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

Use with Warfarin-like Compounds

Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.

Periodic evaluation of prothrombin time should be performed when ULTRAM[®] tablets and warfarin-like compounds are administered concurrently.

Triptans

Based on the mechanism of action of tramadol and the potential for serotonin syndrome, caution is advised when ULTRAM[®] is coadministered with a triptan. If concomitant treatment of ULTRAM[®] with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Drug-Food Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ULTRAM[®] is not recommended for minor pain that may be treated adequately through lesser means where benefit does not outweigh the possible opioid-related side effects.

ULTRAM[®] can be administered without regard to food.

Do not co-administer ULTRAM[®] tablets with other tramadol-containing products

Due to the differences in pharmacokinetic properties, ULTRAM[®] tablets are not interchangeable with tramadol extended-release formulations.

The maximum recommended dose of ULTRAM[®] should not be exceeded.

Recommended Dose and Dosage Adjustment

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.

Adults (18 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 (half ULTRAM[®] scored tablet) 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.) as shown in Table 1.3 below.

Days 1 to 3	Days 4 to 6	Days 7 to 9	Days 10 to 12	Days 13 to 15	Days 16 to 18
Initiate at 25 mg (AM) (half ULTRAM [®] scored tablet)	25 mg b.i.d.	25 mg t.i.d.	25 mg q.i.d.	50 mg t.i.d.	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**.

Use in Renal Impairment

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.

Use in Hepatic Impairment

The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours.

Elderly Patients (> 65 years old)

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.

Pediatric Patients (< 18 years old)

The safety and effectiveness of ULTRAM[®] has not been studied in the pediatric population. Therefore, use of ULTRAM[®] tablets is not recommended in patients under 18 years of age.

Management of Patients Requiring Rescue Medication

If ULTRAM[®] is used as rescue medication in conjunction with extended-release tramadol

tablets, the total daily dose of tramadol should not exceed 400 mg. Fentanyl products should not be used as rescue medication in patients taking ULTRAM[®].

Missed Dose

If a patient misses a dose, they should take their next dose as soon as they remember. If it is almost time for their next dose, they should not take the missed dose. Instead, they should take the next scheduled dose. They should not make up for the missed dose by taking a double dose.

Discontinuation

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms

Symptoms of overdose with ULTRAM[®] are respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest, and death.

Deaths due to overdose have been reported with abuse and misuse of tramadol (see **WARNINGS AND PRECAUTIONS, Drug Abuse, Addiction and Dependence**). Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Treatment

A single or multiple overdose with ULTRAM[®] may be a potentially lethal polydrug overdose, and consultation with a regional poison control centre is recommended.

In treating an overdose of ULTRAM[®], primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

While naloxone will reverse some, but not all, symptoms caused by overdose with tramadol, the risk of seizures is also increased with naloxone administration. Seizures may be controlled with diazepam.

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.

Emptying of the gastric contents is useful to remove any unabsorbed drug.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 **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 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 **Mechanism of Action**). Tramadol is administered as a racemate and both the [-] and [+] 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 **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 1.1 and Table 1.4 below).

Figure 1.1: 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.

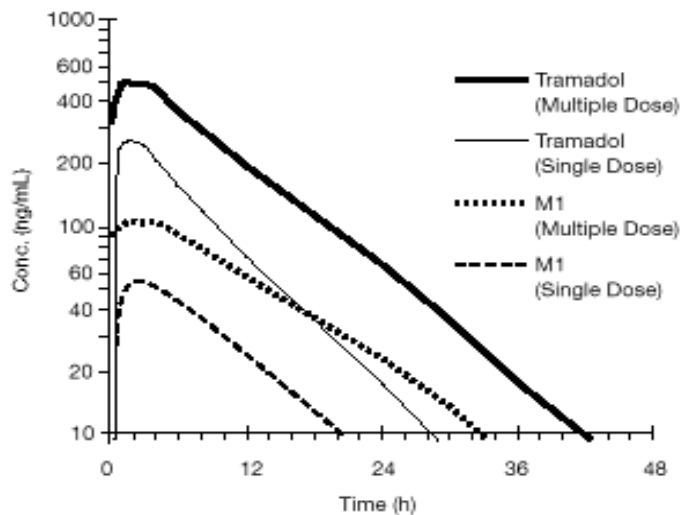


Table 1.4 Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/ Dosage Regimen ^a	Parent Drug/ Metabolite	C _{max} (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

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:

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 **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, and 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. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of

serotonin reuptake inhibitors and MAO inhibitors may enhance the risk of adverse events, including seizure (see **WARNINGS AND PRECAUTIONS**) and serotonin syndrome.

Excretion:

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 and Conditions

Pediatrics:

Pharmacokinetics of ULTRAM[®] tablets have not been studied in pediatric patients below 18 years of age.

Geriatrics:

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.

Hepatic Insufficiency:

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 **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency:

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. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Dispense in a tight container. Store at 15 -30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ULTRAM[®] tablets contain 50 mg of tramadol hydrochloride and are white in colour, capsule-shaped, coated tablet imprinted “ULTRAM” on one side and “06 59” on the scored side. They are available in HDPE bottles of 100 tablets.

Inactive ingredients in the tablet are carnauba wax, corn starch, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

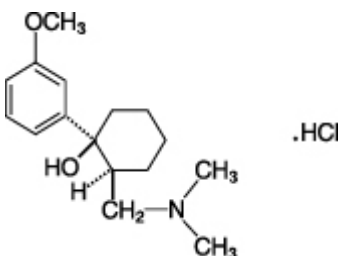
Drug Substance

Proper name: tramadol hydrochloride

Chemical name: (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

Molecular formula and molecular mass: C₁₆ H₂₅ NO₂ ·HCl and 299.84

Structural formula:



Physicochemical properties: Tramadol hydrochloride is a white to off-white, crystalline, odourless powder with a melting point between 180-184°C.

CLINICAL TRIALS

ULTRAM[®] was evaluated in single-dose trials (dental and surgery), multiple-dose, [short-term trials (dental and surgery), long-term trials (chronic malignant and non-malignant pain), and trials evaluating the impact of dose titration on tolerability]. Clinical trials in non-malignant pain included patients with osteoarthritis, low back pain, diabetic neuropathy and fibromyalgia. These trials included a randomized, double-blind, parallel group design, and in each of the single-dose and short-term multiple-dose trials tramadol was compared to a standard reference analgesic (either codeine, ASA/codeine or APAP/propoxyphene), placebo or to both. The active controls were included to establish model sensitivity. The efficacy of tramadol in these trials was established based on Total Pain Relief (TOTPAR), Sum of Pain Intensity Difference (SPID) and time to remedication.

Collectively, a total of 2549 patients with dental pain, 1940 patients with surgical pain, 170 patients with chronic malignant pain, 119 patients with sub-acute low back pain, and 2046 patients with chronic non-malignant pain were enrolled into the 28 efficacy trials. Of the 6824 total patients enrolled into these trials, 4075 were randomized to a tramadol treatment arm.

Study Results

Acute Pain, Single and Multiple Dose 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).

Results of these trials demonstrated statistically superior pain relief for tramadol compared to placebo. Data from these key trials provide information regarding the optimal analgesic dosage range of tramadol.

In single-dose dental trials, tramadol was superior to placebo at doses of 100mg or greater (p#0.05). In addition, tramadol at doses of 100mg or greater were equivalent to or statistically superior to the reference analgesics for Total Pain Relief (TOTPAR) and Sum of Pain Intensity Difference (SPID) across the entire evaluation interval. The results of the multiple-dose short-term trials in acute pain also provide evidence for efficacy of tramadol in the management of acute pain.

Tramadol has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration.

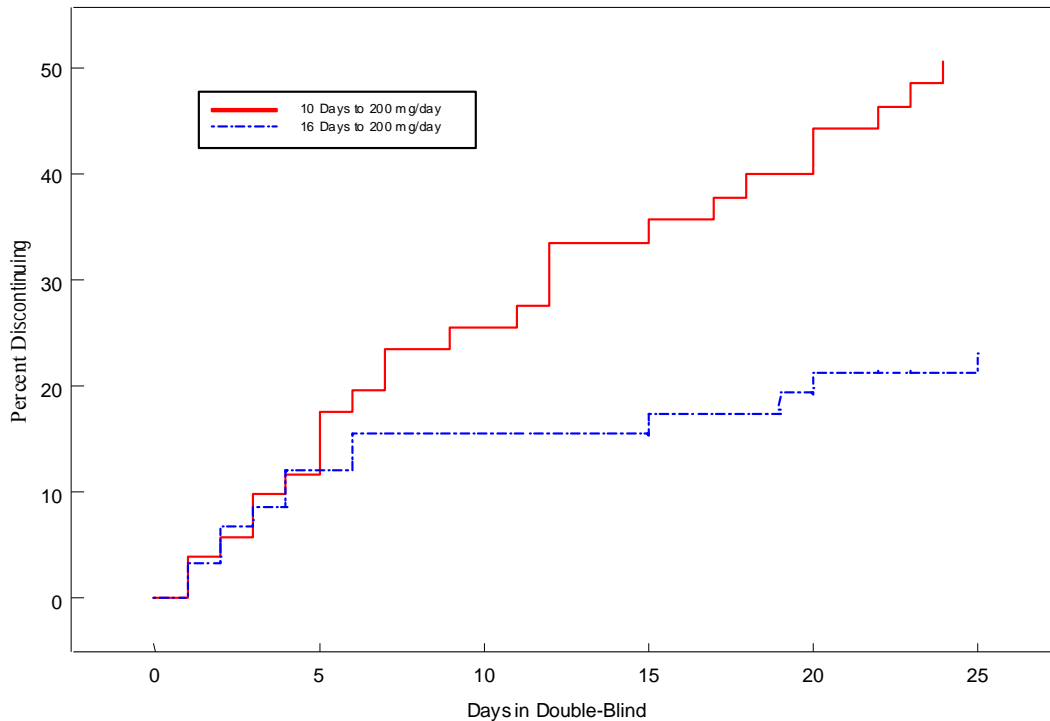
Titration Trials

Two titration trials, TPS DOS and CAPSS-047, provide information regarding appropriate dose titration during chronic use of tramadol. These trials show that a longer titration period can significantly reduce the incidence of adverse events, and the frequency of withdrawal due to adverse events, leading to improved tolerability and overall benefit-risk profile. Efficacy evaluations in these studies suggest that slowing the rate of titration improves tolerability and does not negatively impact on drug efficacy.

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 any cause than did a 10-day titration schedule. See Figure 2.1.

Figure 2.1: Protocol CAPSS-047 – Time to Discontinuation Due to Nausea/Vomiting



DETAILED PHARMACOLOGY

Pharmacodynamics

Tramadol HCl, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol HCl, is a centrally acting synthetic analgesic compound. It is thought to produce its analgesic effect through at least two complementary mechanisms of action: agonist activity at the μ -opioid receptor and weak inhibition of neuronal monoamine reuptake. These dual activities are observed in studies conducted in vitro as well as in nonclinical animal models of antinociception. In studies conducted in vitro, tramadol inhibited binding to native rat μ -opioid receptor at approximately the same concentration at which it blocked the reuptake of norepinephrine and serotonin. The K_1 values for μ -opioid receptor affinity and monoamine reuptake inhibitory activities are 2.1 and $\sim 1 \mu\text{M}$, respectively. Tramadol affinities for recombinant human opioid receptors ($K_1 = 17 \mu\text{M}$) were slightly weaker than those observed at the rat receptors. Apart from analgesia, tramadol may produce a constellation of symptoms similar to that of an opioid.

Tramadol is an efficacious analgesic in a wide variety of standard analgesic models of acute, tonic, chronic, or neuropathic pain. In some of these studies, specific antagonists were used to probe the mechanism of tramadol's antinociceptive action. In contrast to the full blockade of morphine antinociception by naloxone, the antinociceptive action of tramadol in most tests is only partially blocked by naloxone. Furthermore, although the antinociception of morphine is unaffected by the α_2 -adrenergic antagonist yohimbine or the serotonergic antagonist ritanserin, each of these antagonists reduces tramadol's antinociception. These pharmacologic

studies suggest the contribution of both opioid and monoamine mechanisms to tramadol antinociception.

In drug interaction studies carried out with tramadol, a substantial increase in toxicity was found after pretreatment with an MAO inhibitor, tranylcypromine. The antinociceptive effect of the compound was reduced by concomitant administration of barbiturates and atropine, and was virtually eliminated by tranylcypromine. Physostigmine potentiated the antinociceptive effect of a sub-maximal dose of tramadol. Other potential drug interactions based on enzyme induction or displacement from protein binding were thought to be unlikely with tramadol as no inductive effect on liver enzymes has been found for this agent and the protein binding is too low to induce relevant interference with the binding of other compounds.

Pharmacokinetics

Tramadol was rapidly absorbed after oral administration in the mouse, rat, and dog. In dogs, the mean absolute bioavailability of a single 20 mg/kg oral dose of tramadol (Avicel formulation in gelatin capsules) was 81.8%, with maximum plasma concentrations achieved in about one hour. Distribution of radioactivity into tissues was rapid following the intravenous administration of ¹⁴C-labelled tramadol to rats, with the highest concentration of radioactivity found in the liver. Radioactivity levels in the brain were comparable to plasma levels for the first 2 hours post-injection, demonstrating that the drug crosses the blood brain barrier. Concentrations in the kidneys, lungs, spleen, and pancreas were also higher than the serum concentration.

The major metabolic pathway was qualitatively similar for all species studied, including mouse, rat, hamster, guinea pig, rabbit, and man, and involved both Phase I (*N*- and *O*-demethylation and 4-hydroxylation; eight metabolites) and Phase II (glucuronidation or sulfation; thirteen metabolites) reactions. The primary metabolite mono-*O*-desmethyltramadol (M1) has antinociceptive activity. In biochemical studies, (±) mono-*O*-desmethyltramadol and its enantiomers each had greater affinity for opioid receptors and were less potent inhibitors of monoamine uptake than were the corresponding parent compounds.

Excretion was primarily by the renal route in the animal species studied. After oral administration, fecal excretion was approximately 13% in rats and dogs, and 80% of ¹⁴C-labelled tramadol doses were excreted in the urine within 72 to 216 hours of dosing. Amounts of unchanged tramadol excreted in the urine were higher in man (approximately 30% of the dose) than in animals (approximately 1%).

Tramadol is a mild inducer of ethoxycoumarin deethylase activity in the mouse and dog.

TOXICOLOGY

Acute Toxicity

The acute toxicity of tramadol hydrochloride has been examined in the rat. The results of the study are summarized in the following table.

Table 2.1: Acute Toxicity Studies Summary

Species/Strain Age/B.W.	No./Sex/ Group Duration	Route	Vehicle	Dosage Levels (mg/kg)	Lethality	Results
Rat Crl:COBS [®] (WI) BR Age: 7 to 8 wk B.W. Range: 161 to 220 g	5M or 8M single dose	p.o. (gavage)	1% aqueous HPMC	Tramadol: 150 APAP: 300 Tramadol/APAP: 150/300 Vehicle Control: 1% aqueous HPMC (9 mL/kg)	No Mortality	No treatment-related mortality, clinical observations, or effects on body weight.

APAP = acetaminophen; B.W. = body weight; HPMC = hydroxypropylmethylcellulose; M = male; F = female; mo = month; p.o. = oral; wk = week; ↑ = increased; ↓ = decreased

Long-Term Toxicity

Multi-dose toxicity studies were conducted in rat and dog. The following table summarizes the results of the two pivotal multi-dose studies.

Table 2.2: Multi-dose Toxicity Studies - Protocol Summaries/Results

Species/Strain Age/B.W.	No./Group/ Duration/Route	Dosage (mg/kg/day)	Evaluated Parameters	Results
Rat Crl:CD [®] BR, VAF/Plus [®]	10 3 mo p.o. (gavage)	1) Vehicle Control: 0.5% Methocel (10 mL/kg/day) 2) Tramadol/APAP: 7.5/65 22.5/195 45/390 3) Tramadol: 45 4) APAP: 390	Mortality, clinical observations, B.W., food consumption, ophthalmological examination, drug metabolism, hematology, coagulation, clinical chemistry, urinalysis, organ weights, gross pathology, histopathology	<u>Vehicle Control</u> : Four M deaths (attributed to dosing errors); alopecia in both sexes <u>7.5/65</u> : Alopecia in both sexes; 8 liver weights in males <u>22.5/195</u> : One M death (cause of death not determined); alopecia in both sexes; 8 liver weights in males; slightly 8 urine volume in females <u>45/390</u> : Alopecia, 8 salivation, slightly higher urine volume in both sexes; mild treatment related increases in K+ concentration, slightly 9 RBC, 8 MCV, MCH, 8 liver weights, slightly 9 ALT and AST activity and 8 ALP in females <u>45</u> : Alopecia, 8 salivation, in both sexes; slightly 9 ALT and AST activity and 8 ALP in females. <u>390</u> : 8 salivation, slightly higher urine volume in both sexes; 8 liver weights in males; slightly 9 RBC, 8 MCV, MCH in males; alopecia, mild treatment related increases in K+ concentration, slightly 9 ALT and AST activity and 8 ALP in females. Additional findings: (1) higher kidney weights in males dosed with APAP or tramadol/APAP; (2) lower adrenal gland weights in males dosed with tramadol and/or APAP.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APAP = acetaminophen; AST = aspartate aminotransferase; K = potassium; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; mo = month; p.o. = oral; RBC = red blood cell; wk = week; 8 = increased; 9 = decreased

Table 2.2: Multi-dose Toxicity Studies - Protocol Summaries/Results (continued)

Species/Strain Age/B.W.	No./Group/ Duration/Route	Dosage (mg/kg/day)	Evaluated Parameters	Results
Dog Beagle	4 3 mo p.o. (gavage) daily dose divided between two dosing sessions approx. 5.5 h apart	1) Vehicle Control: 0.5% Methocel (1 mL/kg/b.i.d.) 2) Tramadol/APAP: 7.5/65 22.5/195 3) Tramadol: 22.5 4) APAP: 195	Mortality, clinical observations, B.W., estimated food consumption, electrocardiographic/ ophthalmological/ physical examination, drug absorption, hematology. Coagulation, clinical chemistry, urinalysis, gross pathology, microscopic histopathology, organ weights.	<u>7.5/65</u> : NOAEL <u>22.5/195</u> : One male dog was sacrificed moribund on Day 32. 9 activity, discoloured/food emesis, decreased/absent feces, discoloured urine, urine stained coat, jaundice, occult blood in urine, 9 B.W. early in study related to 9 food consumption, slightly to moderately 9 RBC, Hb, and Hct counts, 8 MCV, reticulocyte and platelet counts, slightly to moderately 8 ALT, ALP, GGT, and urine bilirubin values, changes in liver, kidney, bone marrow, spleen, (males) and thymus (males) in both sexes; fine tremor, edema in males; hunched posture, emaciation, ataxia, pallor, 8 total bilirubin, in females <u>22.5</u> : 9 B.W. early in study related to 9 food consumption in both sexes. <u>195</u> : 9 B.W. early in study related to 9 food consumption, slightly to moderately 9 RBC, HB, and HCT counts, 8 MCV, reticulocyte and platelet counts, 8 urine bilirubin, changes in liver, kidney, bone marrow, spleen (males), and thymus (males) in both sexes; slightly 8 ALP, GGT, and total bilirubin values in females

^a Continuation of 4 week dog study results

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APAP = acetaminophen; AST = aspartate aminotransferase; K = potassium; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; mo = month; p.o. = oral; RBC = red blood cell; wk = week; 8 = increased; 9 = decreased; Hb = Hemoglobin; Hct = Hematocrit; GGT = γ -glutamyl transferase

Carcinogenicity

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/m² or 0.36 times the maximum daily human dosage of 246 mg/m²) 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/m², or 0.73 times the maximum daily human dosage).

Mutagenicity

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.

Reproductive Studies

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m²) in male rats and 75 mg/kg (450 mg/m²) in female rats. These dosages are 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m², respectively.

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m²), rats (≥25 mg/kg or 150 mg/m²) and rabbits (≥75 mg/kg or 900 mg/m²) at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages on a mg/m² basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m²) 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/m²), rats (up to 80 mg/kg or 480 mg/m²) or rabbits (up to 300 mg/kg or 3600 mg/m²) 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/m²), 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/m²), respectively.

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/m² 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/m² or 1.9 and higher the maximum daily human dose).

Table 2.3: Reproductive Study – Summary

Species/Strain (No./Group)	Route/ Duration	Dosage (mg/kg/day)	Observations	Results
Rat Crl:CD [®] BR, VAF/Plus [®] 28/group	p.o. (gavage) Gestation Days 6 through 17	1) Vehicle Control: 0.5% Methocel (10 mL/kg/day) 2) Tramadol/APAP: 10/87 25/217 50/434 3) Tramadol: 50	Maternal B.W.; food consumption, clinical signs, and post-mortem exam; number of corpora lutea, implantations, fetuses, resorptions, and pre- and postimplantation loss; fetal weight; fetal alterations	<u>10/87</u> : 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment <u>25/217</u> : 8 alopecia during and after treatment; B.W. loss at treatment initiation; 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment <u>50/434</u> : 8 alopecia during and after treatment; B.W. loss at treatment initiation; 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment; 9 fetal B.W.; 8 supernumerary ribs (attributed to maternal stress, not drug treatment) <u>50</u> : 8 alopecia during and after treatment; B.W. loss at treatment initiation; 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment; 9 fetal B.W. Embryo/fetal NOAEL for tramadol/APAP combination: 25/217 mg/kg/day

APAP = acetaminophen; B.W. = body weight; NOAEL = no-observed-adverse-effect level; p.o. = oral; 8 = increased; 9 = decreased

Dependence Liability

The physical dependence liability potential associated with the chronic use of tramadol has been evaluated in a number of animal studies, including investigations in the mouse, rat, and monkey. A slight degree of antinociceptive tolerance to tramadol evolved in the mouse studies, but there was little or no indication of the development of physical dependence. No evidence of dependence was observed in the rat study. However, in dogs addicted to morphine, withdrawal symptoms were relieved by tramadol. In primate studies, which evaluated the physical dependence and reinforcement properties of tramadol, the physical dependence of the drug was deemed to be low.

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PART III: CONSUMER INFORMATION

PrULTRAM^{®*}
tramadol hydrochloride Tablets, USP

This leaflet is Part III of a three-part "Product Monograph" published when ULTRAM[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ULTRAM[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

ULTRAM[®] (tramadol hydrochloride) is an analgesic. An analgesic is a medication that is used to relieve pain. ULTRAM[®] tablets are prescribed by doctors for the management of moderate pain, or moderately severe pain. Your doctor is the person who knows if ULTRAM[®] tablets are a good choice for you.

What it does:

Tramadol hydrochloride, an opioid analgesic, is a pain reliever that works over several hours to maintain pain relief.

When it should not be used:

You should not use ULTRAM[®] if you are allergic to tramadol, opioids or to any of the non-medicinal ingredients in the product (see **What the nonmedicinal ingredients are**). Contact your doctor immediately if you experience an allergic reaction (e.g. skin rash, hives) or any severe or unusual side effects.

ULTRAM[®] should not be used for minor pain that can be relieved by readily available (over-the-counter) painkillers.

Children under 18 years of age should not take ULTRAM[®] tablets.

Use of ULTRAM[®] tablets in pregnant women is not recommended. It is not clear what effects the medication would have on the fetus.

ULTRAM[®] tablets are 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.

If you have had seizures (convulsions) or have a condition that may put you at increased risk of seizures (epilepsy, head injury, metabolic disorders, alcohol or drug withdrawal), if you are taking monoamine oxidase inhibitors, have an infection of the central nervous system, or are taking antidepressant medication, do not take this medication before discussing your history with your doctor.

Like some pain relievers, ULTRAM[®] tablets may be habit-forming. ULTRAM[®] tablets may not be the best medicine for you if you have had problems with addiction, drug dependence, or drug abuse in the past. Tell your doctor and pharmacist if you have had these conditions before.

What the medicinal ingredient is:

tramadol hydrochloride

What the nonmedicinal ingredients are:

carnauba wax, corn starch, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

What dosage forms it comes in:

50 mg tablets

WARNINGS AND PRECAUTIONS

BEFORE you use ULTRAM[®] be sure to tell your doctor if you have, or had in the past, any other medical conditions (any liver, kidney, or abdominal problems, or if you had a previous head injury), are pregnant or plan to become pregnant, are breast-feeding, and if you are taking any other medications. This will help your doctor to decide whether you should use ULTRAM[®] and what extra care should be taken during its use.

Serious and rarely fatal allergic reactions (e.g. swelling of lips and throat, blistering of skin and/or lips or neck) have been reported in patients receiving therapy with tramadol. Seek medical attention immediately.

Seizures have been reported at therapeutic doses of tramadol and this risk may be increased at doses exceeding the usual upper daily dose limit.

If you are planning surgery, or about to undergo surgery, tell your doctor that you are taking ULTRAM[®].

You should take the following precautions while taking ULTRAM[®] tablets:

Alcohol

You should not take ULTRAM[®] tablets with any alcohol-containing beverages. Also, you should tell your doctor if you drink alcohol regularly, or have a history of alcoholism.

Driving or operating machinery

Do not drive a car or operate other potentially hazardous machinery until you are sure that taking ULTRAM[®] does not make you drowsy.

You must tell your doctor and pharmacist if you are taking any other medications—they will tell you what you should do.

INTERACTIONS WITH THIS MEDICATION

There are other medications that may cause ULTRAM[®] tablets to be less effective, or may cause you to have some side effects or drug reactions.

Drugs that may interact with ULTRAM[®] include:

- Alcohol or other sedative drugs may enhance the drowsiness caused by tramadol;
- Carbamazepine may increase the metabolism of tramadol and reduce the analgesic effect;
- Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), antipsychotics used concomitantly can lower the seizure threshold;
- Digoxin, warfarin or warfarin-like drugs - rare reports of toxicity have been reported when co-administered with tramadol.

You must tell your doctor and pharmacist if you are taking any other medications.

PROPER USE OF THIS MEDICATION**Usual adult dose:**

You may take your ULTRAM[®] tablets with or without food. Take the tablets only as directed by your doctor. It is very important that you do not take more tablets than your doctor advised.

When you first begin taking ULTRAM[®], your doctor may ask you to start slowly and gradually increase the number of tablets you take. **However, you should not take more than 8 tablets per day.** Exceeding these recommendations can result in respiratory depression (shallow, slow breathing), seizures, liver damage, coma, heart stoppage and death. Taking a significant overdose can result in hepatic toxicity.

In patients with kidney problems, the time between doses may be longer. Please speak with your doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The most important sign of overdose is decreased breathing (abnormally slow or weak breathing), or extreme drowsiness.

Discontinuation:

Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms such as anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection and rarely hallucinations.

You should not stop taking ULTRAM[®] all at once if you have been taking it for more than a few days.

To get the full benefit from your treatment, it is important to take ULTRAM[®] tablets as prescribed.

Missed Dose:

It is very important that you do not miss any doses. If you miss a dose, take it as soon as you remember. But, if it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. Do not try to make up for the missed dose by taking a double dose next time. If you miss several doses in succession, talk to your doctor before restarting your medication.

Do not seek additional prescriptions for this medicine from any other doctor unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase, or any other complaint develop as a result of taking ULTRAM[®], contact your doctor immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most medications have some side effects; however, not all people have the same side effects, and some people experience few, if any, side effects. When taking ULTRAM[®] tablets the most common side effects include nausea, vomiting, constipation, headache, dizziness and sleepiness.

Your doctor may order a laxative and stool softener to help relieve your constipation while you are taking ULTRAM[®]. Tell your doctor about these problems if they arise.

If you experience serious symptoms related to an allergic reaction (such as a severe rash or hives), rapid heartbeat, chest pain, dizziness, leg swelling, low blood pressure, change in your mental status, difficulty in breathing, chest tightness, wheezing, fainting, or other serious or unusual symptoms, please consult a doctor or pharmacist immediately.

Physical dependence, abuse and withdrawal reactions have been rarely reported. See withdrawal reactions listed within the 'Discontinuation' section of this leaflet.

This is not a complete list of side effects. For any unexpected effects while taking ULTRAM[®], contact your doctor or pharmacist.

HOW TO STORE IT

ULTRAM[®] tablets should be stored at room temperature (15°C to 30°C).

Do not use ULTRAM[®] tablets after the expiry date. All expired medications should be returned to your pharmacist.

Keep this and all medicines in a safe place away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect[™] Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.jansseninc.ca> or by contacting the sponsor, Janssen Inc., at: 1-800-567-3331

This leaflet was prepared by
Janssen Inc.
Toronto, Ontario
M3C 1L9

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