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:

[Structural Formula]

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 water/n-octanol partition coefficient 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 analgesic compound. 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 an opioid. However, tramadol causes less respiratory depression than morphine at recommended doses (see OVERDOSAGE). 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 [+] 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 Cytochrome P-45O(2D6) and as such is subject to both metabolic induction and 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]

85 **Table 1**

86 **Mean (%CV) Pharmacokinetic Parameters for**

87 **Racemic Tramadol and M1 Metabolite**

88

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)

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90 a SD = Single dose, MD = Multiple dose, p.o.= Oral administration,

91 i.v.= Intravenous administration, q.i.d. = Four times daily

92 b F represents the oral bioavailability of tramadol

93 c Not applicable

94 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. Although not confirmed in humans, tramadol has been shown in rats to cross the blood-brain barrier.

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. Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P450 and as such is subject to both metabolic induction and 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. After a single oral dose of tramadol, concentrations of tramadol were only slightly higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 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 pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Elimination:

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 hr. for tramadol and 19 hr. for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION).

Age:

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 slightly elevated (208 vs. 162 ng/mL) and the elimination half-life is slightly 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, 100, 150 and 200 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. In single-dose models of pain following surgical procedures, 150 mg provided analgesia generally comparable to the combination of acetaminophen 650 mg with propoxyphene napsylate 100 mg, with a tendency toward later peak effect.

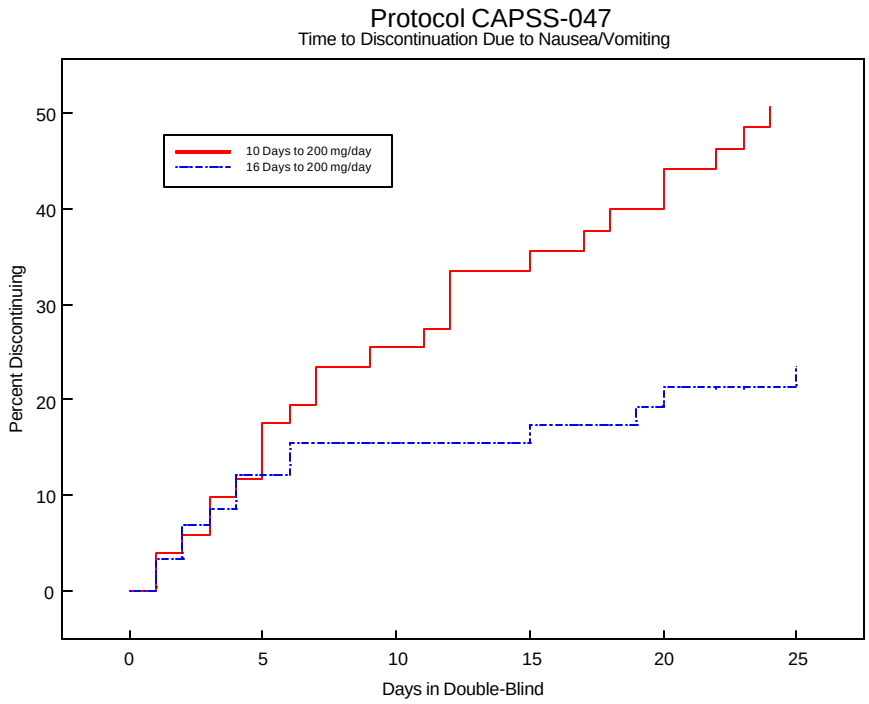
ULTRAM has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving ULTRAM.

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.

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.

CONTRAINDICATIONS

ULTRAM should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

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 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**
- **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. These reactions often occur following the first dose. Other reported reactions include pruritus, hives, bronchospasm, and angioedema. 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).

Use in Opioid-dependent Patients

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. Consequently, in patients with a tendency to opioid abuse or opioid dependence, treatment with ULTRAM is not recommended.

Use with 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, phenothiazines, tranquilizers or sedative hypnotics.

Use with MAO Inhibitors

Use ULTRAM with great caution in patients taking monoamine oxidase inhibitors, because animal studies have shown increased deaths with combined administration.

PRECAUTIONS

Respiratory Depression

Administer ULTRAM cautiously in patients at risk for respiratory depression. When large doses of ULTRAM are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS, Seizure Risk and OVERDOSAGE).

Increased Intracranial Pressure or Head Trauma

ULTRAM should be used with caution in patients with increased intracranial pressure or head injury. 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.

Acute Abdominal Conditions

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

Withdrawal

Withdrawal symptoms may occur if ULTRAM is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhoea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

Patients Physically Dependent on Opioids

ULTRAM is not recommended for patients who are dependent on opioids. Patients who have recently taken substantial amounts of opioids may experience withdrawal symptoms. Because of the difficulty in assessing dependence in patients who have previously received substantial amounts of opioid medication, administer ULTRAM cautiously to such patients.

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 (tramadol hydrochloride tablets) 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 and seizures.

Drug Interactions

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

Concomitant administration of ULTRAM with **carbamazepine** causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine. Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of ULTRAM.

Use with Quinidine

Tramadol is metabolized to M1 by the CYP2D6 P-450 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 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

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.

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice (dosing orally up to 30 mg/kg for approximately two years, although the study was not done with the Maximum Tolerated Dose). This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study.

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

Pregnancy, Teratogenic Effects: *Pregnancy Category C*

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.

Tramadol has been shown to be embryotoxic and fetotoxic in mice, rats and rabbits at maternally toxic doses 3 to 15 times the maximum human dose or higher (120 mg/kg in mice, 25 mg/kg or higher in rats and 75 mg/kg or higher in rabbits), but was not teratogenic at these dose levels. No harm to the fetus due to tramadol was seen at doses that were not maternally toxic.

No drug-related teratogenic effects were observed in progeny of mice, rats or rabbits treated with tramadol by various routes (up to 140

mg/kg for mice, 80 mg/kg for rats or 300 mg/kg for rabbits). 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, a dose that would cause extreme maternal toxicity in the rabbit.

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

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

Use in the Elderly

In subjects over the age of 75 years, serum concentrations are slightly elevated and the elimination half-life is slightly prolonged. The aged also can be expected to vary more widely in their ability to tolerate adverse drug effects. Daily doses in excess of 300 mg are not recommended in patients over 75 (see DOSAGE AND ADMINISTRATION).

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.

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.

Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, 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, Suicidal tendency, Weight loss.

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.

Central Nervous System: Migraine, Speech disorders.

Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis.

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

Sensory: Cataracts, Deafness, Tinnitus.

DRUG ABUSE AND DEPENDENCE

ULTRAM has a potential to cause psychic and physical dependence of the morphine-type (μ-opioid). The drug has been associated with craving, drug-seeking behavior and tolerance development. Cases of abuse and dependence on ULTRAM have been reported. ULTRAM should not be used in opioid-dependent patients. ULTRAM can reinitiate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence, or are chronically using opioids, treatment with ULTRAM is not recommended.

OVERDOSAGE

Cases of overdose with tramadol have been reported. Estimates of ingested dose in foreign fatalities have been in the range of 3 to 5 g. A 3 g intentional overdose by a patient in the clinical studies produced emesis and no sequelae. The lowest dose reported to be associated with fatality was possibly between 500 and 1000 mg in a 40 kg woman, but details of the case are not completely known.

Serious potential consequences of overdosage are respiratory depression and seizure. 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

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

Available data do not suggest that a dosage adjustment is necessary in elderly patients 65 to 75 years of age unless they also have renal or hepatic impairment. For elderly patients **over 75 years old,** not more than 300 mg/day in divided doses as above is recommended. 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 patients with **cirrhosis** is 50 mg every 12 hours. Patients receiving chronic **carbamazepine** doses up to 800 mg daily may require up to twice the recommended dose of ULTRAM.

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

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 controlled room temperature (up to 25◦C, 77◦F).

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ORTHO-McNEIL

PHARMACEUTICAL, INC.

Raritan, New Jersey 08869

U.S. Patents 3,652,589 and 3,830,934

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