

PRODUCT MONOGRAPH

TRIDURAL™

tramadol hydrochloride

Extended-release tablets

100 mg, 200 mg, 300 mg

Opioid Analgesic

Labopharm Inc.
480 Armand-Frappier Blvd.
Laval, Québec
H7V 4B4

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TRIDURAL™ TABLETS

tramadol hydrochloride extended-release tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Extended-release tablets 100 mg, 200 mg, 300 mg	<i>None</i> <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Adults

TRIDURAL™ (tramadol hydrochloride extended-release tablets) is indicated for the management of moderate to moderately severe pain in adults who require treatment for several days or more.

Geriatrics (> 65 years of age):

Healthy elderly subjects aged 65 to 75 years, administered an immediate release formulation of tramadol, have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. TRIDURAL™ 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 TRIDURAL™ has not been studied in the pediatric population. Therefore, use of TRIDURAL™ tablets is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- TRIDURAL™ should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, opioids or any other component of this product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

- TRIDURAL™ 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. TRIDURAL™ may worsen central nervous system and respiratory depression in these patients.
- TRIDURAL™ is contraindicated with concomitant MAO inhibitors (or within 14 days of such therapy).
- TRIDURAL™ is contraindicated in severe renal or hepatic impairment (creatinine clearance of less than 30 ml/min and/or Child-Pugh Class C).

WARNINGS AND PRECAUTIONS

General

TRIDURAL™ (tramadol hydrochloride extended-release tablets) must be swallowed whole and should not be broken, chewed or crushed, since this can lead to the rapid release of tramadol and absorption of a potentially fatal dose of tramadol.

Seizure Risk

Seizures have been reported in patients receiving tramadol hydrochloride within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses above the recommended range. Concomitant use of tramadol hydrochloride increases the seizure risk in patients taking:

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

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

- MAO inhibitors (see **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 tramadol overdose, naloxone administration may increase the risk of seizures.

Anaphylactoid Reactions

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

Drug Abuse, Addiction and Dependence

Tramadol 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 tramadol have been reported. TRIDURAL™ should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence. In patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically abusing opioids, treatment with TRIDURAL™ 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 program to support the safe and effective use of TRIDURAL™ 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 TRIDURAL™ (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 TRIDURAL™ advertising and promotional materials;
- c) Provision of progress reports to TPD, MHPD and HECSB from a drug abuse surveillance program for TRIDURAL™
- d) Assurance that health-care education activities on pain management with TRIDURAL™ 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;
- e) Reassessment of the risk management program 2 years post product launch.

TRIDURAL™ is intended for oral use only. Extended-release tablets may be abused by breaking, crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

TRIDURAL™ should not be used to treat the symptoms of opioid withdrawal 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 TRIDURAL™ 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 tramadol discontinuation include: panic attacks, severe anxiety and paresthesias.

Clinical experience suggests that signs and symptoms of withdrawal may be avoided by tapering medication when discontinuing tramadol therapy. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. Clinical experience suggests that withdrawal symptoms may be relieved by reinstatement of tramadol therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

Risk of Overdosage

Serious potential consequences of overdosage with TRIDURAL™ 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 TRIDURAL™ for patients who are suicidal or addiction-prone.

TRIDURAL™ 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

TRIDURAL™ should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving TRIDURAL™ (see **WARNINGS AND PRECAUTIONS, Respiratory Depression**).

Respiratory Depression

Administer TRIDURAL™ cautiously in patients at risk for respiratory depression, such as patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, or hypercapnia. In these patients alternative non-opioid analgesics should be considered and opioids should be employed only under careful medical supervision at the lowest effective dose. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see **WARNINGS AND PRECAUTIONS, Seizure Risk and OVERDOSAGE**).

Interaction with Central Nervous System (CNS) Depressants

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

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

In Vitro Dissolution Studies of Interaction with Alcohol

Increasing concentrations of ethanol resulted in a decrease in the rate of release of TRIDURAL™ tablets.

Use with Alcohol

TRIDURAL™ should not be used concomitantly with alcohol consumption. The use of TRIDURAL™ in patients with liver disease is not recommended.

Use in Ambulatory Patients

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

Use with Serotonin Reuptake Inhibitors

Concomitant use of tramadol products with SSRIs increases the risk of adverse events, including seizure and serotonin syndrome (see **WARNINGS AND PRECAUTIONS, Seizure Risk** and **DRUG INTERACTIONS**).

Acute Abdominal Conditions

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

Use in Drug and Alcohol Addiction

TRIDURAL™ is an opioid with no approved use in the management of addictive disorders.

Carcinogenesis and Mutagenesis

See animal data in Toxicology section.

Special Populations

Hepatic/Biliary/Pancreatic Impairment:

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 hours for tramadol and 19 hours for M1).

TRIDURAL™ is contraindicated in patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Renal Impairment:

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. TRIDURAL™ is contraindicated in severe renal impairment. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose (see **DOSAGE AND ADMINISTRATION**).

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. Therefore, TRIDURAL™ should not be used during pregnancy and labour, unless in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus.

Chronic use during pregnancy may lead to physical dependence and post-partum 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. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol during post-marketing.

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

Nursing Women:

TRIDURAL™ 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.

Pediatrics (< 18 years of age):

The safety and use of TRIDURAL™ in patients under 18 years of age has not been established. The use of TRIDURAL™ in the pediatric population is not recommended.

Geriatrics (> 65 years of age):

In general, caution should be used when selecting the dose for an elderly patient. The elimination half-life of tramadol may be prolonged in patients over 75 years, thereby increasing the potential for adverse events. Usually, dose administration should start 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 (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In clinical trials, TRIDURAL™ was administered to 1013 patients aged 65 years and older. Of those, 89 patients were 75 years of age and older. Comparable incidence rates of patients experiencing adverse events were observed for patients older than 65 years of age compared with younger patients (< 65 years of age), except constipation for which the incidence was higher in older patients. TRIDURAL™ should be used with caution in patients older than 75 years of age (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS**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.

TRIDURAL™ was administered to a total of 2707 subjects (2406 patients and 301 healthy volunteers) during clinical studies, including four randomized double-blind studies (treatment ≥ 12 weeks) and two open-label long-term studies (treatment up to 12 months) in patients with moderate to severe pain due to osteoarthritis of the knee. A total of 1901 patients were exposed to TRIDURAL™ during 12-week studies, 493 for a 6-month period and 243 for a 12-month period. A total of 1013 patients were 65 years and older, including 89 patients 75 years of age and older. A summary of adverse events occurring at an incidence of 1% or more is given in Table 1, which includes all events, whether considered by the clinical investigator to be related to the study drug or not.

Table 1. Percentage of Patients with Incidence of Adverse Events \geq 1% from Three 12-week Placebo-Controlled Studies (MDT3-002, MDT3-003 and MDT3-005)

Adverse Events	Tridural™			Total N = 1095	Placebo N = 668
	100 mg N = 216	200 mg N = 311	300 mg N = 530		
Any TEAE	125 (57.9%)	184 (59.2%)	302 (57.0%)	690 (63.0%)	338 (50.6%)
Ear and labyrinth disorders					
Vertigo	3 (1.4%)	3 (1.0%)	8 (1.5%)	27 (2.5%)	3 (0.4%)
Gastrointestinal disorders					
Abdominal pain	2 (0.9%)	5 (1.6%)	8 (1.5%)	17 (1.6%)	7 (1.0%)
Abdominal pain upper	3 (1.4%)	4 (1.3%)	9 (1.7%)	18 (1.6%)	4 (0.6%)
Constipation	21 (9.7%)	38 (12.2%)	53 (10.0%)	143 (13.1%)	27 (4.0%)
Diarrhea	6 (2.8%)	1 (0.3%)	10 (1.9%)	21 (1.9%)	20 (3.0%)
Dry mouth	7 (3.2%)	17 (5.5%)	7 (1.3%)	38 (3.5%)	8 (1.2%)
Dyspepsia	3 (1.4%)	6 (1.9%)	4 (0.8%)	13 (1.2%)	7 (1.0%)
Nausea	29 (13.4%)	50 (16.1%)	88 (16.6%)	202 (18.4%)	39 (5.8%)
Vomiting	8 (3.7%)	19 (6.1%)	36 (6.8%)	71 (6.5%)	6 (0.9%)
General disorders and administration site conditions					
Fatigue	6 (2.8%)	10 (3.2%)	9 (1.7%)	29 (2.6%)	6 (0.9%)
Pain exacerbated	6 (2.8%)	3 (1.0%)	6 (1.1%)	18 (1.6%)	16 (2.4%)
Weakness	3 (1.4%)	5 (1.6%)	4 (0.8%)	12 (1.1%)	1 (0.1%)
Infections and infestations					
Influenza	2 (0.9%)	1 (0.3%)	8 (1.5%)	11 (1.0%)	3 (0.4%)
Nasopharyngitis	4 (1.9%)	7 (2.3%)	7 (1.3%)	20 (1.8%)	18 (2.7%)
Upper respiratory tract infection	3 (1.4%)	5 (1.6%)	6 (1.1%)	16 (1.5%)	17 (2.5%)
Urinary tract infection	2 (0.9%)	3 (1.0%)	6 (1.1%)	12 (1.1%)	10 (1.5%)
Investigations					
Weight decreased	1 (0.5%)	5 (1.6%)	11 (2.1%)	20 (1.8%)	1 (0.1%)
Metabolism and nutrition disorders					
Anorexia	5 (2.3%)	4 (1.3%)	11 (2.1%)	27 (2.5%)	2 (0.3%)
Musculoskeletal and connective tissue disorders					
Arthralgia	2 (0.9%)	3 (1.0%)	8 (1.5%)	15 (1.4%)	14 (2.1%)
Nervous system disorders					
Dizziness	18 (8.3%)	31 (10.0%)	59 (11.1%)	119 (10.9%)	21 (3.1%)
Headache	13 (6.0%)	18 (5.8%)	26 (4.9%)	64 (5.8%)	43 (6.4%)
Somnolence	12 (5.6%)	23 (7.4%)	26 (4.9%)	82 (7.5%)	13 (1.9%)
Tremor	1 (0.5%)	3 (1.0%)	6 (1.1%)	11 (1.0%)	1 (0.1%)
Psychiatric disorders					
Anxiety NEC	1 (0.5%)	6 (1.9%)	4 (0.8%)	11 (1.0%)	1 (0.1%)
Insomnia	3 (1.4%)	9 (2.9%)	11 (2.1%)	25 (2.3%)	8 (1.2%)
Skin and subcutaneous tissue disorders					
Pruritus	11 (5.1%)	16 (5.1%)	23 (4.3%)	60 (5.5%)	7 (1.0%)
Sweating increased	1 (0.5%)	10 (3.2%)	16 (3.0%)	38 (3.5%)	6 (0.9%)
Vascular disorders					
Hot flushes	1 (0.5%)	3 (1.0%)	7 (1.3%)	12 (1.1%)	1 (0.1%)

* Due to the difference in study design of MDT3-005, only the results of the double-blind phase of the study are presented and the dose specific results include maintenance period data only.

The majority of patients who experienced the most common adverse events ($\geq 1\%$) reported mild to moderate symptoms. Less than 3% of adverse events were rated as severe. Overall, onset of these adverse events usually occurred within the first two weeks of treatment.

Adverse events with an incidence of <1.0% (whether considered by the clinical investigator to be related to the study drug or not):

Blood and lymphatic system disorders: anaemia, lymphadenopathy, thrombocytopenia.

Cardiac disorders: acute myocardial infarction, angina pectoris, angina unstable, atrial fibrillation, bradycardia, cardiovascular disorder, palpitations, sinus tachycardia, tachycardia.

Ear and labyrinth disorders: cerumen impaction, ear congestion, ear discomfort, ear pain, labyrinthitis, tinnitus.

Endocrine disorders: hypothyroidism.

Eye disorders: cataract, dry eyes, eye pain, eyelid disorder, lacrimation increased, photopsia, scleral haemorrhage, blurred vision, visual disturbance.

Gastrointestinal disorders: abdominal discomfort, abdominal distension, lower abdominal pain, abdominal tenderness, change in bowel habit, constipation aggravated, diverticulitis, dyspepsia aggravated, dysphagia, faecal impaction, feces discoloured, flatulence, food poisoning, gastric irritation, gastritis, gastrointestinal haemorrhage, gastrointestinal irritation, gastro-oesophageal reflux disease, hiccups, lip blister, loose stools, pancreatitis aggravated, rectal haemorrhage, rectal prolapse, retching, small intestinal obstruction, toothache.

General disorders and administration site conditions: asthenia, chest pain, chest tightness, fall, feeling abnormal, feeling cold, inflammation localised, inflammation, influenza like illness, lethargy, malaise, mass, oedema peripheral, pain, rigors, thirst.

Hepatobiliary disorders: biliary tract disorder, cholelithiasis.

Immune system disorders: hypersensitivity, seasonal allergy.

Infections and infestations: abscess limb, bladder infection, bronchitis, ear infection, erysipelas, foot infection fungal, fungal infection, gastroenteritis, gastroenteritis viral, gastrointestinal infection, helicobacter infection, herpes simplex, herpes zoster, laryngitis acute, nail fungal infection, otitis externa, otitis media, otitis media serous, pharyngitis, respiratory tract infection viral, sinusitis, stye, tooth abscess, tooth infection, tracheitis, vaginosis fungal, viral infection, wound infection.

Injury, poisoning and procedural complications: abrasion, arthropod bite, back injury, blister, concussion, eye injury, face injury, hand fracture, head injury, joint sprain, laceration, ligament injury, limb injury, muscle injury, muscle strain, neck injury, postoperative wound complication, soft tissue injury, tendon injury, wrist fracture.

Investigations: alanine aminotransferase decreased, alanine aminotransferase increased, aspartate aminotransferase decreased, aspartate aminotransferase increased, blood amylase increased, blood calcium increased, blood cholesterol increased, blood creatinine increased, blood glucose abnormal, blood glucose increased, blood in stool, blood potassium abnormal, blood pressure increased, blood urea increased, body temperature increased, cardiac murmur, c-reactive protein increased, gamma-glutamyltransferase increased, haematocrit decreased, haematocrit increased, haemoglobin decreased, haemoglobin increased, low density lipoprotein increased, lymphocyte count increased, mammogram abnormal, mean platelet volume decreased, neutrophil count decreased, protein total decreased, red blood cell count decreased, red blood cell count increased, red blood cell sedimentation rate increased, red cell distribution width increased, white blood cell count increased.

Metabolism and nutrition disorders: decreased appetite, dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycaemia, hyperlipidemia, hypertriglyceridaemia, hyperuricaemia, hypocalcaemia, hypokalaemia.

Musculoskeletal and connective tissue disorders: back disorder, back pain, bone pain, bone spur, bursitis, ganglion, groin pain, joint crepitation, joint disorder, joint stiffness, joint swelling, muscle cramps, muscle spasms, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, neck stiffness, osteoarthritis aggravated, osteopenia, osteoporosis, pain in limb, plantar fasciitis, polyarthralgia, rheumatoid arthritis, temporomandibular joint arthralgia, tendonitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps): benign breast neoplasm, breast cancer invasive, breast cancer, thyroid neoplasm, uterine fibroids.

Nervous system disorders: ataxia, burning sensation, disturbance in attention, dysarthria, dysgeusia, gait abnormal, headache aggravated, hypoaesthesia, mental impairment, migraine, neuralgia, paraesthesia, sedation, sinus headache, sleep apnoea syndrome, syncope.

Psychiatric disorders: abnormal behaviour, agitation, bipolar disorder, confusion, depression, emotional disturbance, euphoric mood, indifference, irritability, libido decreased, nervousness, sleep disorder.

Renal and urinary disorders: calculus renal, difficulty in micturition, dysuria, haematuria, micturition urgency, nocturia, renal impairment, renal pain, urinary frequency, urinary hesitation, urinary incontinence, urinary retention.

Reproductive system and breast disorders: dysmenorrhoea, erectile dysfunction, genital pruritus female, menometrorrhagia, prostatitis, sexual dysfunction, vaginal cyst, vaginal discharge.

Respiratory, thoracic and mediastinal disorders: asthma aggravated, asthma, chest wall pain, cough, crackles lung, dry throat, dyspnoea, epistaxis, nasal congestion, nasal oedema, pharyngolaryngeal pain, productive cough, rhinitis allergic, rhinitis, rhinorrhea, rhonchi, sinus congestion, sinus pain, throat irritation.

Skin and subcutaneous tissue disorders: acne, cold sweat, contusion, dermatitis allergic, dermatitis contact, dermatitis, dermatitis aggravated, dermatosis, dry skin, eczema exacerbated, eczema, erythema, hyperkeratosis, ingrowing nail, night sweat, pallor, piloerection, prurigo, pruritus generalised, rash, rash pruritic, rosacea, skin ulcer, urticaria.

Surgical and medical procedures: cardiac pacemaker replacement, colon polypectomy, endodontic procedure, foot operation, hernia repair, lesion excision, tumour excision.

Vascular disorders: aortic aneurysm, deep venous thrombosis, flushing, haematoma, hot flushes aggravated, hypertension aggravated, hypertension, hypotension, orthostatic hypotension, poor peripheral circulation, vascular insufficiency, wound haemorrhage.

Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials where clinical abnormalities were recorded (n = 106), the following abnormalities were reported: Sedimentation rate increased (0.7%), glucose abnormalities (0.5%), GGT increased (0.4%).

The following abnormalities occurred in 0.2% of patients: cholesterol abnormalities, LDH increased, uric acid increased, hemoglobin decreased, red cell count decreased.

The following abnormalities occurred in <0.1% of patients: hematocrit decreased, alanine aminotransferase increased, aspartate aminotransferase increased, urea increased, liver function tests abnormal.

The following abnormalities were single occurrences: alanine aminotransferase decreased, aspartate aminotransferase decreased, amylase increased, bilirubin increased, calcium increased, creatinine increased, potassium abnormal, C-Reactive Protein increased, hematocrit increased, hemoglobin increased, low density lipoprotein increased, lymphocyte count decreased, mean platelet volume decreased, neutrophil count decreased, platelet count decreased, protein total decreased, red cell count increased, red cell distribution width increased, white cell count increased.

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 SSRIs 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 behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. Tramadol is associated with craving and tolerance development.

A Risk Management program to support the safe and effective use of TRIDURAL™ 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 TRIDURAL™ (i.e., not listed under a schedule to the CDSA) in its advertising or promotional activities;
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- d) Assurance that health-care education activities on pain management with TRIDURAL™ 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;
- e) Reassessment of the risk management program 2 years post product launch.

Withdrawal Symptoms

Withdrawal symptoms may occur if tramadol is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with tramadol hydrochloride discontinuation include: panic attacks, severe anxiety, and paresthesias.

Withdrawal symptoms have been studied in 325 patients, 3 and 7 days after discontinuation of treatment with TRIDURAL™. The majority of symptoms were mild to moderate in nature. Onset of the post-treatment adverse events occurred more frequently within the first 3 days after treatment was stopped. Less than 1% of patients taking TRIDURAL™ met the DSM-IV criteria for a diagnosis of opioid withdrawal.

Clinical experience suggests that signs and symptoms of withdrawal may be avoided by tapering medication when discontinuing tramadol therapy.

DRUG INTERACTIONS

Overview

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when it 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.

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with TRIDURAL™ may affect the metabolism of tramadol leading to altered tramadol exposure.

Drug-Drug Interactions

MAO Inhibitors

Tramadol 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 reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions (see **WARNINGS AND PRECAUTIONS**).

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.

Use with Carbamazepine

Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of TRIDURAL™ and carbamazepine is not recommended.

Use with Quinidine

Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol products 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.

Inhibitors or Inducers of CYP3A4

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort may affect the metabolism of tramadol, leading to altered tramadol exposure.

Use with Cimetidine

Concomitant administration of tramadol immediate-release tablets with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the TRIDURAL™ dosage regimen with cimetidine is recommended.

Protease Inhibitors, e.g., ritonavir

Co-administered ritonavir may increase the serum concentration of tramadol, resulting in tramadol toxicity.

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 reports of alteration of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for tramadol, periodic evaluation of prothrombin time should be performed when TRIDURAL™ tablets and warfarin-like compounds are administered concurrently.

Drug-Food Interactions

Co-administration with food did not significantly change the overall exposure to tramadol; however, peak plasma concentrations increased. In the presence of food, the availability and controlled-release properties of TRIDURAL™ tablets were maintained with no evidence of dose dumping. TRIDURAL™ was administered either with breakfast or before breakfast in all clinical trials.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TRIDURAL™ (tramadol hydrochloride) 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.

TRIDURAL™ tablets must be swallowed whole and should not be broken, chewed or crushed, since this can lead to the rapid release of tramadol and absorption of a potentially fatal dose of tramadol.

Due to possible differences in pharmacokinetic properties, TRIDURAL™ tablets are not interchangeable with other tramadol-containing products.

The maximum recommended daily dose of TRIDURAL™ should not be exceeded.

TRIDURAL™ is contraindicated in patients with severe hepatic or renal impairment.

Do not co-administer TRIDURAL™ tablets with other tramadol containing products.

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

TRIDURAL™ extended-release tablets should be taken once a day at breakfast. The tablets should be swallowed whole with liquid and not split, chewed, dissolved or crushed.

TRIDURAL™ tablets have a continuous release of active ingredient over 24 hours: a repeat dosage within 24 hours is not recommended.

Recommended Dose and Dosage Adjustment

Adults

Treatment with TRIDURAL™ should be initiated at a dose of 100 mg/day. Daily doses should be titrated by 100 mg/day increments every 2 days (i.e. start 200 mg/day on day 3 of therapy) to achieve a balance between adequate pain control and tolerability for the individual patient. For patients requiring the 300 mg daily dose, titration should take at least 4 days (i.e. 300 mg/day on day 5). The daily dose and titration should be individualized for each patient. Therapy should be continued with the lowest effective dose. TRIDURAL™ should not be administered at a dose exceeding 300 mg per day.

The correct dosage for any individual patient is that which controls the pain for a full 24 hours with no or tolerable side effects.

Patients Not Receiving Opioids at the Time of Initiation of Tramadol Treatment: The usual initial dose of TRIDURAL™ for patients who have not previously received opioid analgesics is 100 mg q24h.

Patients Currently Receiving Other Tramadol Formulations: Patients currently receiving other oral immediate-release tramadol preparations may be transferred to TRIDURAL™ tablets at the same or lowest nearest total daily tramadol dosage.

Geriatric patients (65 years of age and older)

In general, dose selection for patients over 65 years of age, who may have decreased hepatic or renal function, or other concomitant diseases, should be initiated cautiously, usually starting at the low end of the dosing range. TRIDURAL™ should be administered with greater caution at the lowest effective dose in patients over 75 years, due to the potential for greater frequency of adverse events in this population.

Pediatric Use

The safety and effectiveness of TRIDURAL™ has not been studied in the pediatric population. Therefore, the use of TRIDURAL™ is not recommended in patients under 18 years of age.

Renal and Hepatic Disease

TRIDURAL™ is contraindicated in patients with:

- creatinine clearance less than 30 mL/min,
- severe hepatic impairment.

The elimination half-life of tramadol and its active metabolite may be prolonged in mild to moderate renal and/or hepatic disease. A starting dose of 100 mg daily is recommended, and upward dosage titration should be done with careful monitoring.

Management of Breakthrough Pain

If episodes of breakthrough pain are encountered with appropriate adjustments of TRIDURAL™ dose, acetaminophen or ibuprofen may be given. If immediate release tramadol is used for breakthrough pain, the total daily dose of tramadol should not exceed 300 mg. Selection of breakthrough medication should be based on individual patient conditions.

Missed Dose

If a patient forgets to take one or more doses, they should take their next dose at the normal time and in the normal amount.

Discontinuation

Withdrawal symptoms may occur if TRIDURAL™ 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 tramadol discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that signs and symptoms of withdrawal may be avoided by tapering medication when discontinuing tramadol therapy (see **DRUG ABUSE, ADDICTION AND DEPENDENCE, Withdrawal Symptoms**).

OVERDOSAGE

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. 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.

Symptoms of Overdose:

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Treatment of Overdose

A single or multiple overdose with TRIDURAL™ may be a potentially lethal drug overdose, and consultation with a regional poison control centre is recommended.

In treating an overdose, 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 overdosage with tramadol, 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.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see **Pharmacokinetics**).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of TRIDURAL™.

Apart from analgesia, tramadol 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, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacokinetics

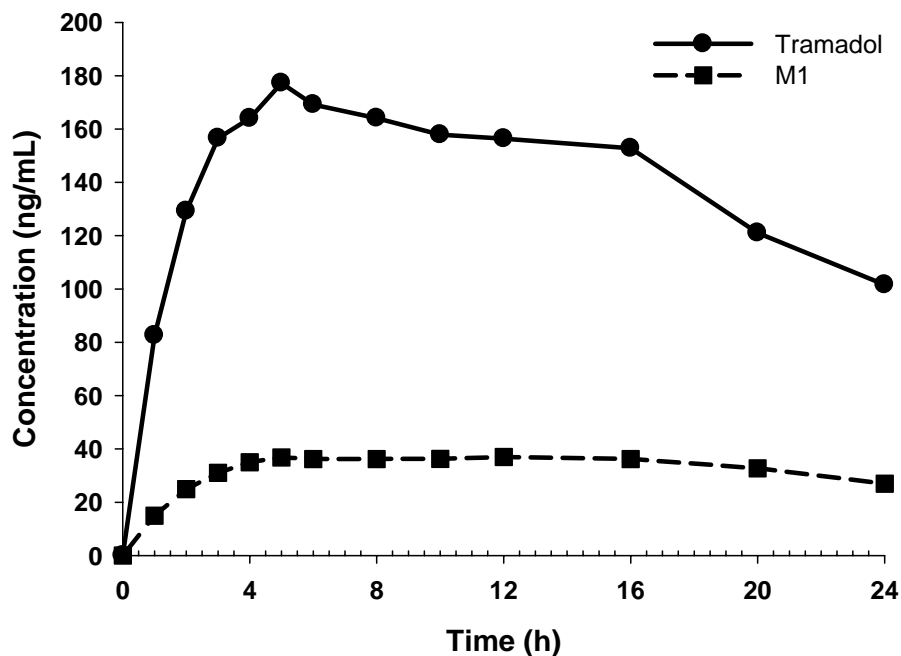
The analgesic activity of tramadol hydrochloride is due to both parent drug and the M1 metabolite (see **CLINICAL PHARMACOLOGY, Mechanism of Action**).

In a single-dose study, the dose adjusted bioavailability of the 100 mg, 200 mg and 300 mg tablets were equivalent confirming a linear pharmacokinetic response (in relation to both tramadol and O-desmethyltramadol) over this range of strengths. Dose proportionality of the 100 mg, 200 mg and 300 mg tablets has been demonstrated.

Absorption:

Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70%. There is no lag time in drug absorption following administration of TRIDURAL™. TRIDURAL™ exhibits a plasma/time concentration profile with a sharp initial slope similar to immediate-release tramadol tablets followed by a sustained release phase. This behavior is due to the two phases of drug release which work together to provide a smooth plasma concentration/time profile (Figure 1).

Figure 1. Mean Tramadol and M1 Plasma Concentrations over the 24-Hour Dosing Interval Following a Single Oral Dose of TRIDURAL™ 200 mg



The mean peak steady-state plasma concentrations of tramadol and M1 after multiple dose administration of TRIDURAL™ 200 mg tablets to healthy subjects are attained at about 4.3 h and 7.4 h, respectively (Table 2).

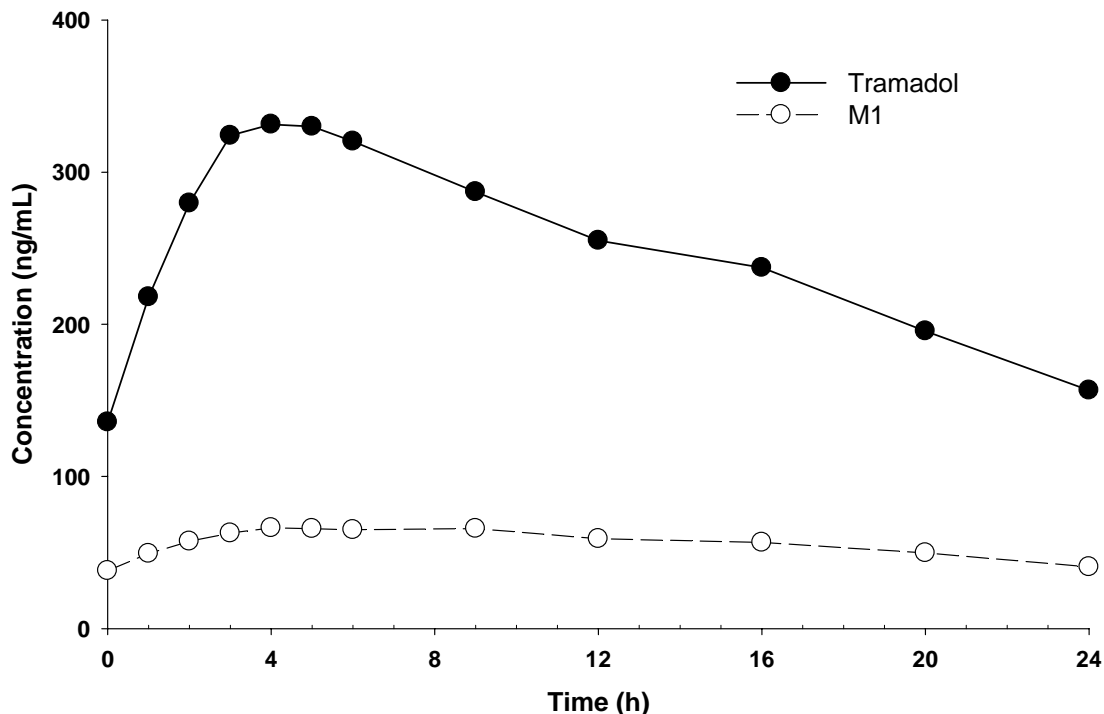
Table 2. Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=26)

Pharmacokinetic Parameter	Tramadol	M1 Metabolite
	TRIDURAL™ 200 mg Tablet Once-Daily	TRIDURAL™ 200 mg Tablet Once-Daily
AUC ₀₋₂₄ (ng·h/mL)	5991 (22)	1361 (27)
C _{max} (ng/mL)	345 (21)	71 (27)
C _{min} (ng/mL)	157 (31)	41 (30)
T _{max} (hr)*	4.0 (3.0 – 9.0)	5.0 (3.0 – 20.0)
Fluctuation (%)	77 (26)	53 (29)

*T_{max} is presented as Median (Range)

Steady-state levels with TRIDURAL™ were reached within 48 hours (Figure 2). This is clinically meaningful in that it forms the basis for the titration schedule in all clinical studies and the dosing recommendations related to titration (see **DOSAGE AND ADMINISTRATION**).

Figure 2. Mean Tramadol Plasma Concentrations at Steady-State Following Oral Administration of TRIDURAL™ 200 mg Once Daily



Food Effect:

Co-administration with food did not significantly change the overall exposure to tramadol; however, peak plasma concentrations increased. TRIDURAL™ was administered either with breakfast or before breakfast in all efficacy and safety clinical trials.

In Vitro Dissolution Studies of Interaction with Alcohol:

Increasing concentrations of ethanol resulted in a decrease in the rate of release of TRIDURAL™ tablets.

Distribution:

The volume of distribution of tramadol is 2.6 and 2.9 L/kg in males and females, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20%. Protein binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism:

Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see **DRUG INTERACTIONS**).

Elimination:

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. 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. After single administration of TRIDURAL™, the mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.5 ± 1.5 and 7.5 ± 1.4 hours, respectively.

Special Populations and Conditions**Renal Insufficiency:**

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. TRIDURAL™ has not been studied in patients with severe renal impairment (creatinine clearances of less than 30 mL/min), and therefore should not be used in these patients (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Renal Impairment** and **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 Insufficiency:

TRIDURAL™ is contraindicated in patients with severe hepatic impairment. The elimination half-life of tramadol and its active metabolite may be prolonged in patients with hepatic impairment. TRIDURAL™ has not been studied in patients with severe hepatic impairment and, therefore should not be used (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic Impairment** and **DOSAGE AND ADMINISTRATION**).

Geriatrics:

Healthy elderly subjects aged 65 to 75 years, administered an immediate-release formulation of tramadol, have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. The elimination half-life of tramadol may be prolonged in patients over 75 years, thereby increasing the potential for adverse events. Adjustment of the daily dose is recommended for patients older than 75 years (see **DOSAGE AND ADMINISTRATION**).

Gender:

Following a 100 mg IV dose of tramadol, plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females. This difference is not likely to be clinically significant; therefore, dosage adjustment based on gender is not recommended.

Pediatrics:

Pharmacokinetics of TRIDURAL™ tablets have not been studied in pediatric patients below 18 years of age.

STORAGE AND STABILITY

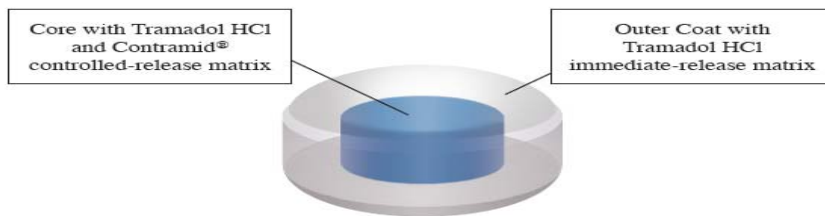
Store at room temperature (15° – 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRIDURAL™ extended-release tablets contain 100 mg, 200 mg or 300 mg of tramadol hydrochloride. The tablets are white in color. The inactive ingredients in the tablet are colloidal silicon dioxide, Contramid® (modified starch), hydrogenated vegetable oil, magnesium stearate, polyvinyl acetate, povidone, sodium lauryl sulfate, xanthan gum, shellac glaze, isopropyl alcohol, iron oxide black, n-butyl alcohol, propylene glycol and ammonium hydroxide.

TRIDURAL™ tablets are comprised of a dual-matrix delivery system with an outer compression coat (containing tramadol hydrochloride) providing immediate release characteristics and a controlled-release core containing tramadol hydrochloride and Contramid®, which provides the controlled-release characteristics (Figure 3).

Figure 3 Tablet Showing the Immediate Release Matrix (lighter outer part) and the Extended Release Matrix (dark inner part)



TRIDURAL™ (tramadol hydrochloride extended-release) tablets are supplied in a number of packages and dose strengths:

100-mg, white, beveled edge, round biconvex tablets, plain on one side and printed “LP 100” in black ink on the other side.

- Bottle of 30 tablets
- Bottle of 90 tablets
- Bottle of 100 tablets
- Bottle of 500 tablets
- Blister pack of 20 tablets, 2 cards of 10 single-dose units

200-mg, white, beveled edge, round biconvex tablets, plain on one side and printed “LP 200” in black ink on the other side.

- Bottle of 30 tablets
- Bottle of 90 tablets
- Bottle of 100 tablets
- Bottle of 500 tablets
- Blister pack of 20 tablets, 2 cards of 10 single-dose units

300-mg, white, beveled edge, round biconvex tablets, plain on one side and printed “LP 300” in black ink on the other side.

- Bottle of 30 tablets
- Bottle of 90 tablets
- Bottle of 100 tablets
- Bottle of 500 tablets
- Blister pack of 20 tablets, 2 cards of 10 single-dose units

Product Monograph available upon request.

Labopharm Inc.
Laval, Québec H7V 4B4

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PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

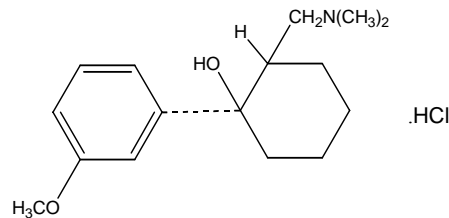
Proper name: tramadol hydrochloride

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

Molecular formula: $C_{16}H_{25}NO_2 \cdot HCl$

Molecular weight: 299.8

Structural formula:



Physicochemical properties: Tramadol hydrochloride is a white crystalline powder that is freely soluble in water and methanol.

CLINICAL TRIALS

TRIDURAL™ efficacy was studied in three 12-week placebo-controlled, randomized, double-blind, studies (MDT3-002, MDT3-003 and MDT3-005) in patients with moderate to severe pain due to osteoarthritis. No rescue medication was permitted in any of the studies.

In one placebo-controlled study (MDT3-005), the key measure of analgesic efficacy was the Pain Intensity on Numerical Rating Scale (PI-NRS) (Table 3). In the other two studies, the three co-primary measures of analgesic efficacy were the Patient Global Rating of Pain, the WOMAC Pain subscale and the WOMAC Physical Function subscale (Table 4).

Study Demographics and Trial Design

Table 3. Study Demographics, Trial Design and Results of Study MDT3-005

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean age (Years)	Gender
Study MDT3-005	Randomised, double-blind, placebo-controlled, parallel group, titration to effect-TRIDURAL™ vs. placebo	TRIDURAL™ 200-300 mg/day vs. placebo, oral, 12 weeks	n= 646 randomised	TRIDURAL™: 62±9 Placebo: 62±9	Males: 37% Females: 63%
Primary Endpoint	Associated value and statistical significance for TRIDURAL™ vs baseline		Associated value and statistical significance for placebo vs baseline		
Pain intensity (11 point numerical rating scale)*	TRIDURAL™ Score		Placebo Score		
	Baseline	7.2 ± 1.6	Baseline	7.2 ± 1.6	
	Last Visit	4.3 ± 2.5	Last Visit	4.8 ± 2.4	
	Improvement from baseline: 2.9 ± 2.5 95% CI [2.7; 3.1]		Improvement from baseline: 2.4 ± 2.4 95% CI [2.1; 2.7]		
Improvement from baseline TRIDURAL™ vs. Placebo, p = 0.0157					

* Pain Intensity Numerical Rating Scale: 11 points (0 = No pain, 10 = Worst possible pain)

Table 4. Study Demographics, Trial Design and Results of Study MDT3-003

Study #	Trial Design	Dosage Route of Administration and Duration	Study Subjects (n=number)	Mean age (Years)	Gender
Study MDT3-003	Randomised, double-blind, placebo-controlled, parallel group, titration to randomized dose	TRIDURAL™ 100-300 mg/day vs. placebo, oral, 12 weeks	n=552	TRIDURAL™: 61±9 Placebo: 61±10	Males: 38% Females: 62%
Primary Endpoint	Patient Rating	TRIDURAL™		Placebo	
		200 mg	300 mg		
Patient Global Rating of Pain (Categorical scale: not effective , effective or very effective at the end of treatment)	Very effective' n and (%)	32/107 (30%)	45/105 (43%)	50/224 (22%)	
	Effective' n and (%)	44 /107 (41%)	37/105 (35%)	85/224 (38%)	
	Not effective' n and (%)	31/107 (29%)	23/105 (22%)	88/224 (40%)	
	P value for the difference TRIDURAL™ vs. Placebo				
	200 mg: p = 0.0017		300 mg: p < 0.0001		
WOMAC Pain subscale¹ (5 X 100 mm VAS)	TRIDURAL™		Placebo		
	Baseline	284 ± 82 mm		314 ± 97 mm	
	Last Visit	160 ± 129 mm	172 ± 138 mm	202 ± 149 mm	
	Improvement from baseline	123 ± 129 mm (43%)	143 ± 136 mm (46%)	100 ± 146 mm (32%)	
	Difference active vs. placebo	11%	13%	-	
	P value for the difference TRIDURAL™ vs. Placebo				
	200 mg: p = 0.0504		300 mg: p = 0.0162		
WOMAC Physical Function subscale² (17 X 100 mm VAS)	TRIDURAL™		Placebo		
	Baseline	999 ± 323 mm		1096 ± 349 mm	
	Last Visit ³	493 mm	543 mm	668 mm	
	Improvement from baseline ³	367 mm (45%)	421 mm (46%)	267 mm (27%)	
	Difference active vs. placebo	11%	12%	-	
	P value for the difference TRIDURAL™ vs. Placebo⁴				
	200 mg: p= 0.0450		300 mg: p= 0.0211		

¹ WOMAC Pain subscale score: 5 questions, 100 mm VAS each (0 – no pain to 100 mm – extreme pain). Subscale score range (0 to 500 mm).

² WOMAC Physical Function subscale score: 17 questions, 100 mm VAS each (0 – no difficulty to 100 mm – extreme difficulty). Subscale score range (0 to 1700 mm).

³ Median values presented due to non-normal distribution of the data

⁴ non-parametric ANCOVA

In study MDT3-002, on the Patient Global Rating of Pain, 73% of patients randomized to TRIDURAL™ 300 mg rated it as effective or very effective, compared to 59% of patients randomized to Placebo. The difference between TRIDURAL™ 300 mg and Placebo was statistically significant ($p= 0.0008$). Due to a high placebo response, the other study parameters did not achieve statistical significance.

DETAILED PHARMACOLOGY

Pharmacodynamics

Tramadol hydrochloride, 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 ^{14}C -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-desmethylation (M1) has antinociceptive activity. In biochemical studies, (\pm) 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, faecal 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 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

Contramid®

Contramid® (hydroxypropyl distarch phosphate), an excipient present in TRIDURAL™ 100 mg, 200 mg and 300 mg tablets, is responsible for the controlled-release characteristics of the TRIDURAL™ tablets. TRIDURAL™ 100 mg, 200 mg and 300 mg tablets have already been approved in 24 European countries and 2 Latin American countries and are currently commercially available in many of them. Contramid® is also utilized as a food additive and its use is permitted in unlimited proportions. It meets the specifications for food-modified starch as stated in the current editions of the USP-NF 30 and the Food Chemicals Codex, as well as in 21 CFR part 172.892. The safety profile of Contramid® has been established in one acute toxicity study and one Bacterial Reverse Mutation assay (Ames test). These findings confirm the toxicological findings regarding hydroxypropyl distarch phosphate in the literature.

The acute toxicity study performed in rats showed that the oral LD₅₀ of Contramid® was greater than 2000 mg/kg. There were no clinical or gross necropsy findings. This result was consistent with high oral LD₅₀ values determined for distarch phosphate. The LD₅₀ of distarch phosphate in mice, rats, guinea pigs, rabbits and cats was found to be greater than 24, 35, 18, 10 and 9 g/kg respectively. Absence of mutagenic potential of Contramid® at concentrations up to 5000 µg/plate was shown in the reverse bacterial mutation assay (Ames test). Available data from the literature from several short-term studies show no significant adverse effects in rats fed daily for up to 3 months with a diet containing up to 25% of hydroxypropyl distarch phosphate. Data from long-term studies did not provide any evidence of carcinogenicity of hydroxypropyl

distarch phosphate at dietary levels up to 62%, which is equivalent to 37 g per rat per day, and in animals fed three days a week. A diet of up to 62% modified starches had no effects on fertility, litter size or embryonic or pre-weaning mortality, and histological examination of the F3 generation showed no treatment-related anomalies.

Tramadol

The acute toxicity of tramadol hydrochloride has been examined in the mouse, rat, rabbit, guinea pig and dog. Summarized LD₅₀ values are presented in the following table.

Table 5. Acute Toxicity Studies Summary

Species	Oral LD ₅₀ Values (mg/kg)	s.c.	i.v.	i.m.	i.p.	rectal
Mouse*	328-785	197-265	47-68	179-184	178-200	–
Rat	151-572	240-293	56	–	–	540-662
Rabbit	300-450	–	20-40	100-150	–	160
Guinea pig	850-897	23-250	–	–	–	–
Dog	100-450	–	>50 < 100	>50 < 100	–	–

s.c. = subcutaneous; i.v. = intravenous; i.m. = intramuscular; i.p. = intraperitoneal

*Signs of toxicity of tramadol in male mice: sedation in low doses followed by hypermotility, straub tail, slight tremor, exophthalmos, clonic convulsions, cyanosis.

Long-Term Toxicity

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

Table 6. Multidose Toxicity Studies Summary

Species/Strain Age/B.W.	No./Sex/ Group Duration	Route	Dosage Levels (mg/kg)	Lethality	Evaluated Parameters	Results
Rat Wistar 18 mo Age: 30-35 days B.W. M: 83 g F: 78 g	20 M + 20 F /dose 18 mo	Oral	Tramadol 0 7.5 15 30	4/20 M, 0/20 F 1/20 M, 0/20 F 2/20 M, 2/20 F 1/20 M, 2/20 F	Mortality, B.W., food and water consumption, clinical signs, haematology, fecal blood, urinalysis, organ weights, histopathology	Except for body weight loss and increased food and water consumption, no treatment dose-related effects were observed.
Dog Beagle Age: approx 11 mo B.W. M: 10.4-13.6 kg F: 6.6-10.4 kg	4F + 4M /dose 52-weeks	Oral	Tramadol: 0 10 24 40	1/4 M*	Mortality, B.W., food and water consumption, clinical signs, haematology, fecal blood, urinalysis, organ weights, histopathology	No treatment related effects were observed except for slightly reduced weight gain and food intake in the females of all treatment groups.

B.W. = body weight; M = male; F = female; mo = month

*All animals survived except one mid-dose male was sacrificed, week 37, due to recurring urinary obstruction due to large bladder stone. This was not considered treatment related.

Carcinogenicity

Two carcinogenicity studies were conducted: a 24-month oral mouse study and a 30-month oral rat study. These studies examined approximately 4 times the human therapeutic daily dose. There was no evidence that tramadol is carcinogenic. In mice, chronic administration of tramadol at doses of 0, 7.5, 15, or 30 mg/kg/day did not affect life span or enhance tumour formation. There was a slight but statistically significant increase in the incidence of commonly occurring tumours in aged mice. Rats treated at the same dosage levels for 30 months did not show any evidence of carcinogenic potential.

Mutagenicity

Tramadol hydrochloride did not demonstrate any mutagenic activity in the Ames test, the CHO/HPRT assay, or in the mouse lymphoma assay in the absence of metabolic activation. Weekly mutagenic results were obtained in the presence of metabolic activation in the mouse lymphoma assay, but these were secondary to high levels of induced cytotoxicity. In vivo studies (micronucleus test in the mouse, rat, and hamster) were negative. A bone marrow cytogenetics test in hamsters was negative as was a dominant lethal test in mice.

Reproductive Studies

The potential of tramadol to produce reproductive toxicity was evaluated in a series of six main studies in mice, rats and rabbits. The results of these studies indicated that tramadol had no effect on fertility in male or female rats, even at toxic oral dose levels (up to 50 mg/kg in males and 75 in females). Tramadol did not induce teratogenicity in mice, rats, or rabbits given up to 140, 80, or 300 mg/kg, respectively. Embryo/fetal toxicity, consisting of slight decreases in fetal weight, and/or variations in bone ossification, occurred at tramadol doses 3 to 15 times the maximum human dose or higher, but only in the presence of maternal toxicity. Maternal toxicity generally consisted of decreased body weight gain in conjunction with decreased food consumption.

In peri- and postnatal studies in the rat, maternal toxicity occurred in dams treated with tramadol gavage doses of 8mg/kg and higher. Signs of toxicity included decreased body weight gain and reduced food consumption. A rebound in these parameters did occur during lactation, suggesting some adaptation to the effects of the drug, although weight gain of treated dams continued to lag behind those controls throughout the remainder of the study. At doses of 20 mg/kg and higher, clinical signs such as exophthalmia and dilated pupils increased; alopecia increased at doses of 40 mg/kg and greater. Progeny of dams receiving 50 mg/kg or higher had decreased body weights. At doses of 80 mg/kg or higher, decreased pup survival during early lactation was noted.

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

TRIDURAL™
tramadol hydrochloride
Extended-release Tablets

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

ABOUT THIS MEDICATION

What the medication is used for:

TRIDURAL™ (tramadol hydrochloride) is an oral tablet that slowly releases tramadol (an opioid analgesic) over a 24 hour period to manage pain that is expected to persist for several days or more. Your doctor is the person who knows if TRIDURAL™ tablets are a good choice for you.

What it does:

TRIDURAL™ is a medicine used to treat moderate to moderately severe pain and should relieve your pain and help the pain relief last longer.

Your pain may increase or decrease from time to time and your doctor may need to change the amount of tramadol you take daily (daily dosage).

When it should not be used:

TRIDURAL™ should not be used if:

- Your doctor did not prescribe it for you
- You are allergic to tramadol, opioids or to any of the non-medicinal ingredients in the product (see **What the non-medicinal ingredients are**). Contact your doctor immediately if you experience an allergic reaction (e.g. skin rash, hives) or any severe or unusual side effects.
- You are consuming large amounts of alcohol or taking excessive amounts of other drugs that can depress respiration/breathing and consciousness
- You are taking, or have taken within the past 2 weeks, a monoamine oxidase inhibitor medication (e.g., Nardil, Parnate);
- You have severe kidney or liver disease.

TRIDURAL™ should not be used for minor pain that can be relieved by readily available (over-the-counter) pain killers.

Children under 18 years of age should not take TRIDURAL™ tablets.

Use of TRIDURAL™ tablets in pregnant women is not recommended. It is not clear what effects the medication would have on the fetus.

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

Like some pain relievers, TRIDURAL™ tablets may be habit forming. TRIDURAL™ 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:

TRIDURAL™ tablets contain tramadol hydrochloride.

What the non-medicinal ingredients are:

Non-medicinal ingredients for TRIDURAL™ are: ammonium hydroxide, colloidal silicon dioxide, Contramid® (modified starch), hydrogenated vegetable oil, iron oxide black, isopropyl alcohol, magnesium stearate, n-butyl alcohol, polyvinyl acetate, povidone, propylene glycol, shellac glaze, sodium lauryl sulfate, and xanthan gum.

What dosage forms it comes in:

TRIDURAL™ extended-release tablets are available in three strengths, each containing 100 mg, 200 mg or 300 mg of tramadol hydrochloride, the active ingredient.

WARNINGS AND PRECAUTIONS

BEFORE you use TRIDURAL™ 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 TRIDURAL™ 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 TRIDURAL™.

You should take the following precautions while taking TRIDURAL™ tablets:

Alcohol

You must not consume alcohol while taking TRIDURAL™ tablets as it may increase the chance of experiencing dangerous side effects. 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 TRIDURAL™ does not make you drowsy.

Other medications

You should not take other medications that contain tramadol while you are taking TRIDURAL™ tablets.

There are also other drugs, such as tranquilizers, antidepressants, hypnotics, sleeping pills, or other analgesics, that cause some serious reactions when taken by someone who is also taking TRIDURAL™ tablets. You must tell your doctor and pharmacist if you are taking any other over-the-counter or prescription medications – they will tell you what you should do.

INTERACTIONS WITH THIS MEDICATION

There are other medications that may cause TRIDURAL™ tablets to be less effective, or may cause you to have some side effects or drug reactions.

Drugs that may interact with TRIDURAL™ 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 reuptakeinhibitors (SSRIs), antipsychotics used concomitantly can lower the seizure threshold;
- Protease inhibitors (e.g., ritonavir) - co-administration may increase the blood levels of tramadol;
- 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:

TRIDURAL™ should be swallowed whole with a sufficient quantity of liquid and not split, chewed, dissolved or crushed since this can lead to the rapid release and absorption of an excessive dose of tramadol, which can seriously harm you.

TRIDURAL™ should be taken once daily at breakfast, at approximately the same time every day. Do not repeat your dose within 24 hours.

If your pain worsens, making you uncomfortable, contact your doctor - she/he may decide that it is necessary to adjust your daily dosage. **You should not take more than the maximum recommended dose of 300 mg of TRIDURAL™ per day.** Exceeding this recommendation can result in respiratory depression (shallow, slow breathing), seizures, coma, heart stoppage and death

Your dose of TRIDURAL™ will be clearly labelled on the medication bottle. Be sure to follow the directions on the label exactly; this is very important. Do not increase or decrease your dose without

consulting your doctor. If your dosage is changed by your doctor, be sure to write it down at the time your doctor calls or sees you, and follow the new directions exactly. Review your pain regularly with your doctor to determine if you still need TRIDURAL™.

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

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 TRIDURAL™ all at once if you have been taking it for more than a few days.

Overdose:

The most important sign of overdose is decreased breathing (abnormally slow or weak breathing), or extreme drowsiness. If you accidentally take an overdose of TRIDURAL™, contact your doctor and/or the nearest hospital or Emergency Room, and/or Poison Control Centre immediately, even though you may not feel sick.

Missed Dose:

It is very important that you do not miss any doses. If you miss one or more doses, take the next dose at the normal time and in the normal amount. Do not take two doses at once, unless your doctor tells you to. 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 TRIDURAL™ 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. When taking TRIDURAL™ tablets the most common side effects include nausea, vomiting, constipation,

headache, dizziness and sleepiness. Slower titration may be an effective way to reduce adverse effects. Your doctor may order a laxative and stool softener to help relieve your constipation while you are taking TRIDURAL™. Tell your doctor about these problems if they arise. If you experience serious symptoms or any other unusual symptoms, tell your doctor immediately.

If you experience any 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 rapid heartbeat, 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 TRIDURAL™ contact your doctor or pharmacist.

HOW TO STORE IT

TRIDURAL™ tablets should be stored at room temperature (15°C to 30°C).

Keep TRIDURAL™ in a secure place to prevent theft and misuse.

Do not give any of it to anyone other than the person for whom it was prescribed, since it may seriously harm them.

Do not use TRIDURAL™ tablets after the expiry date. All expired medications should be returned to your pharmacist.

Keep this and all medicines in a safe place, and out of the reach of children. Accidental overdose with TRIDURAL™ by a child is dangerous and may result in death.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadtmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.labopharm.com> or by contacting the sponsor, Labopharm Inc., at: 1-800-686-1017

This leaflet was prepared by
Labopharm Inc.
Laval, Québec H7V 4B4

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