

PRODUCT MONOGRAPH

PrZytram XL[®]

Tramadol Hydrochloride

Controlled Release Tablets – 150, 200, 300 and 400 mg

Professed Standard

Opioid Analgesic

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION3
INDICATIONS AND CLINICAL USE.....3
CONTRAINDICATIONS3
WARNINGS AND PRECAUTIONS.....4
ADVERSE REACTIONS.....9
DRUG ABUSE, ADDICTION AND DEPENDENCE12
DRUG INTERACTIONS12
DOSAGE AND ADMINISTRATION14
OVERDOSAGE16
ACTION AND CLINICAL PHARMACOLOGY17
STORAGE19
SPECIAL HANDLING INSTRUCTIONS19
DOSAGE FORMS, COMPOSITION AND PACKAGING19

PART II: SCIENTIFIC INFORMATION21
PHARMACEUTICAL INFORMATION.....21
CLINICAL TRIALS.....21
DETAILED PHARMACOLOGY24
TOXICOLOGY25
REFERENCES26

PART III: CONSUMER INFORMATION.....30

Pr Zytram XL®

Tramadol Hydrochloride Controlled Release (CR) Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Controlled release tablets / 150 mg, 200 mg, 300mg, 400mg	hydrogenated vegetable oil, hypromellose, lactose, magnesium stearate, polyethylene glycol, talc, titanium dioxide

INDICATIONS AND CLINICAL USE

Adults

Zytram XL® (tramadol HCl controlled release tablets) is indicated for:

- the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more.

Geriatrics (>65 years of 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. **Zytram XL** should be administered with greater caution in patients over 75 years, due to the greater potential for adverse events in this population (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**) sections.

Pediatrics (<18 years of age)

The safety and efficacy of **Zytram XL** has not been studied in the pediatric population. Therefore, use of **Zytram XL** tablets is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to tramadol, opioids, or to any ingredient in the formulation;
- In any situation where opioids are contraindicated, including acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients;
- Concomitant MAO inhibitors (or within 14 days of such therapy);
- Severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C).

WARNINGS AND PRECAUTIONS

General

Zytram XL[®] (tramadol HCl controlled release tablets) must be swallowed whole and should not be broken, chewed, dissolved 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 within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Opioids.

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

- 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 seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these rare reactions do occur it is often following the first dose. Other reported 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 tramadol (see **CONTRAINDICATIONS**).

Drug Abuse, Addiction and Dependence

Tramadol has a potential to cause psychic and physical dependence of the morphine-type (Φ -opioid). The drug has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol have been reported. **Zytram XL** tablets should not be used in opioid-dependent patients. Tramadol can re-initiate physical dependence in patients who have been previously dependent or chronically using other opioids. In patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically using opioids, treatment with **Zytram XL** 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 **Zytram XL** 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 **Zytram XL** (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 **Zytram XL** advertising and promotional materials;
- c) Provision of progress reports to TPD, MHPD and HECSB from a drug abuse surveillance program for **Zytram XL**;
- d) Assurance that health-care education activities on pain management with **Zytram XL** 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.

Zytram XL is intended for oral use only. **Zytram XL** could 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.

Zytram XL should not be used in opioid-dependent patients since it cannot suppress morphine withdrawal symptoms, even though it is an opioid agonist.

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

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

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

Withdrawal Symptoms

Withdrawal symptoms may occur following abrupt discontinuation of therapy. 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.

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 **Zytram XL** 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 **Zytram XL** for patients who are suicidal or addiction prone.

Zytram XL 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.

Increased Intracranial Pressure or Head Trauma

Zytram XL should be used with caution in patients with increased intracranial pressure or head injury, since the respiratory depressant effects of opioid receptor agonism include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and such effects may be markedly exaggerated in these patients. Also, 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 tramadol (see **WARNINGS AND PRECAUTIONS, Respiratory Depression**).

Respiratory Depression

Administer **Zytram XL** cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use

cautiously because it may precipitate seizures (see **WARNINGS AND PRECAUTIONS, Seizure Risk** and **OVERDOSAGE**).

Interaction With Central Nervous System (CNS) Depressants

Zytram XL 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. Tramadol increases the risk of CNS and respiratory depression in these patients.

Zytram XL 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 alcohol in the dissolution medium, resulted in a slight decrease in the rate of release of tramadol from **Zytram XL** tablets. The clinical significance of the slight decrease in dissolution rate is unknown.

Use in Ambulatory Patients

Zytram XL 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 Re-uptake Inhibitors (SSRIs)

Use **Zytram XL** with caution in patients taking SSRIs. Concomitant use of **Zytram XL** with SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

Acute Abdominal Conditions

As may occur with other analgesics, the administration of **Zytram XL** may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Drug and Alcohol Addiction

Zytram XL is an opioid with no approved use in the management of addictive disorders. Its approved usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of moderate to moderately severe chronic pain requiring continuous treatment with an opioid analgesic.

Carcinogenesis and Mutagenesis

See animal data in Toxicology section.

Special Populations

Renal Impairment: **Zytram XL** is contraindicated in patients with severe renal impairment. The elimination half-life of tramadol and its active metabolite may be prolonged in patients with renal impairment.

Hepatic/Biliary/Pancreatic Impairment: **Zytram XL** 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.

Pregnant Women: The safety of tramadol in pregnancy has not been established. Therefore, **Zytram XL** should not be used in pregnant women, prior to or during labour, unless in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus.

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. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing reports with tramadol hydrochloride immediate-release products.

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

Nursing Women: Tramadol and its metabolites are found in small amounts in human breast milk. Since its safety in infants and newborns has not been studied, tramadol should not be administered for obstetrical preoperative medication, post delivery analgesia or at any time during breast feeding.

Pediatrics (<18 years of age): The safety and efficacy of **Zytram XL** has not been studied in the pediatric population. Therefore, use of **Zytram XL** tablets is not recommended in patients under 18 years of age.

Geriatrics (>65 years of age): In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function; of concomitant disease and multiple drug therapy. The elimination half-life of tramadol may be prolonged in patients over 75 years, thereby increasing the potential for adverse events.

Monitoring and Laboratory Tests

Not Applicable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The pre-marketing development program for **Zytram XL**[®] (tramadol HCl controlled release tablets) included exposure to a total of 1,213 participants in seven randomized, double-blind controlled clinical trials (n = 1028) and one six-month open-label trial (n = 185). 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.

The most common adverse effects with **Zytram XL** are constipation, dizziness, headache, nausea, somnolence and vomiting. These are common effects associated with other drugs with opioid-agonist activity. Slower titration – a 7 day as compared to a 2 day schedule, may be an effective strategy to reduce adverse effects.

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.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Table 1 - Adverse Events Reports in Zytram XL Clinical Trials (≥1%)

	Number of Patients	% of Patients N = 1,213
Body as a Whole		
Headache	132	10.9
Asthenia	93	7.7
Sweating	69	5.7
Pain	26	2.1
Central Nervous System		
Dizziness	214	17.6
Somnolence	191	15.7
Depression	12	1.0
Insomnia	24	2.0
Tremor	13	1.1
Vasodilation	24	2.0

	Number of Patients	% of Patients N = 1,213
Digestive System		
Constipation	274	22.6
Nausea	357	29.4
Vomiting	135	11.1
Diarrhea	54	4.5
Abdominal pain	30	2.5
Anorexia	42	3.5
Dry mouth	61	5.0
Dyspepsia	49	4.0
Flatulence	15	1.2
Respiratory System		
Cough increased	11	1.0
Pharyngitis	17	1.4
Skin and Appendages		
Pruritus	27	2.2

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Body as a Whole: abnormal gait, accidental injury, back pain, chest pain, chills and fever, flu syndrome, infection, malaise, photosensitivity, syncope.

Cardiovascular: angina pectoris, arrhythmia, atrial flutter, hypertension, migraine, palpitation, peripheral vascular disorder, phlebitis, tachycardia.

Digestive: abnormal stools, bloating, diverticulitis, eructation, gastric motility reduced, gastritis, gastroenteritis, gastrointestinal hemorrhage, hiccup, irritable bowel syndrome, laryngitis, melena, pancreatitis, rectal disorder, rectal hemorrhage, thirst, tongue disorder, weight decrease.

Endocrine: abnormal ejaculation, impotence, libido decreased.

Hemolytic & Lymphatic: hemolytic anemia, liver function test abnormal.

Metabolic & Nutritional: alkaline phosphatase increased, hypercholesteremia, hyperglycemia, hyperlipemia, peripheral edema, hepatic enzymes increased.

Musculoskeletal: arthritis, arthrosis, bursitis, cramps, fatigue, gout, joint disorder, knee effusion, muscle pain, muscle weakness, myalgia, myopathy, pathological fracture, tendon disorder.

<u>Nervous:</u>	abnormal coordination, abnormal dreams, abnormal thinking, amnesia, anxiety, apathy, ataxia, carpal tunnel syndrome, confusion, depersonalization, emotional liability, euphoria, hallucinations, hyperesthesia, hypertonia, loss of smell, malaise, myoclonus, nervousness, paresthesia, vertigo.
<u>Respiratory:</u>	asthma, bronchospasm, dyspnea, epistaxis, hemoptysis, hyperventilation, pneumonia, respiratory disorder, rhinitis, sinusitis.
<u>Skin:</u>	acne, dermatitis, dry skin, eczema, flushing, gooseflesh, herpes simplex, herpes zoster, purpura, rash, sebaceous cyst.
<u>Special Senses:</u>	amblyopia, blepharitis, cellulitis, conjunctivitis, dry eyes, eustachian tube dysfunction, eye pain, halitosis, lacrimation disorder, otitis media, sore mouth, taste perversion, tinnitus, tooth disorder, vision abnormal.
<u>Urogenital:</u>	albuminuria, calcium crystalluria, cystitis, dysuria, enlarged prostate, gynecomastia, hematuria, nocturia, polyuria, renal pain, urinary retention, urinary tract infection, urine abnormality, vaginal hemorrhage.

Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials where clinical abnormalities were recorded (n= 245), the following laboratory abnormalities were reported: ALT (3%), AST (2%), alkaline phosphatase (4%), creatinine (2%), BUN (4%), potassium (2%), sodium (1%), bilirubin (0.4%), basophils (0.4%), eosinophils (0.4%), lymphocytes (3%), monocytes (3%), neutrophils (1%), LDH (4%), RBC (3%), platelets (2%), WBC (2%), glucose (0.4%), triglycerides (1%) and TSH (0.4%).

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

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

Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRI's and MAOIs.

DRUG ABUSE, ADDICTION AND DEPENDENCE

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

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

A Risk Management program to support the safe and effective use of **Zytram XL** 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 **Zytram XL** (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 **Zytram XL** advertising and promotional materials;
- c) Provision of progress reports to TPD, MHPD and HECSB from a drug abuse surveillance program for **Zytram XL**;
- d) Assurance that health-care education activities on pain management with **Zytram XL** 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 **Zytram XL** discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be relieved by reinstatement of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

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 re-uptake 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.

Carbamazepine

Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Since carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of **Zytram XL** (tramadol HCl controlled release tablets) and carbamazepine is not recommended.

Quinidine

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

Inhibitors of CYP2D6

Inhibitors of CYP2D6 (e.g., quinidine, fluoxetine, paroxetine, amitriptyline) may inhibit the metabolism of tramadol, resulting in increased serum concentrations of tramadol and decreased concentrations of its O-demethylated metabolite (M1). Co-administration of quinidine did not diminish the analgesic effect of tramadol in human experimental pain models.

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.

Cimetidine

Concomitant administration of tramadol and cimetidine is associated with a small prolongation of the half-life of tramadol, but no alteration of the **Zytram XL** dosage regimen is recommended.

Digoxin

Digoxin toxicity has occurred rarely during co-administration of digoxin and tramadol.

Protease inhibitors, e.g., ritonavir

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

Warfarin and other coumarin anticoagulants

Alteration of the effect of warfarin, including elevation of prothrombin times, has been reported rarely during co-administration of warfarin and tramadol. While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when **Zytram XL** tablets and warfarin-like compounds are administered concurrently.

Drug-Food Interactions

In the presence of food, the availability and controlled-release properties of **Zytram XL** tablets were maintained with no evidence of dose dumping.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Zytram XL (tramadol HCl controlled release tablets) is not recommended for minor pain, or acute short-term pain that may be treated adequately through lesser means where benefit does not outweigh the possible opioid-related side effects.

Due to possible differences in pharmacokinetic properties, **Zytram XL** tablets are not interchangeable with other tramadol-containing products.

The maximum recommended daily dose of **Zytram XL** should not be exceeded.

Zytram XL is contraindicated in patients with severe hepatic or renal impairment.

Administration

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

Recommended Dose and Dosage Adjustment

General: Zytram XL is designed to allow for once daily dosing, i.e., dosing at 24-hourly intervals. Treatment with Zytram XL should generally be initiated at the lowest available dose (150 mg).

As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. It is recommended that doses be slowly titrated - dosage adjustments generally separated by 7 days, to higher doses to minimize side effects.

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 Zytram XL for patients who have not previously received opioid analgesics is 150 mg q24h.

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

Adults: The usual initial dose is one 150 mg tablet daily. If adequate pain relief is not achieved, the dosage should be gradually titrated upwards. The maximum recommended daily dose is 400 mg.

Elderly Patients (> 65 years old): Since the elimination half-life of tramadol may be prolonged in elderly patients, a starting dose of 150 mg daily is recommended. Upward dosage titration should be done with careful monitoring. Zytram XL should be administered with greater caution in patients over 75 years, due to the greater potential for adverse events in this population

Pediatrics (< 18 years old): The safety and efficacy of Zytram XL has not been studied in the pediatric population. Therefore, use of Zytram XL tablets is not recommended in patients under 18 years of age.

Patients with Renal or Hepatic Insufficiency: The elimination half-life of tramadol and its active metabolite may be prolonged in these patient populations. A starting dose of 150 mg daily is recommended. Upward dosage titration should be done with careful monitoring. Tramadol is contraindicated in patients with severe renal impairment and/or severe hepatic impairment. (creatinine clearance less than 30 mL/min and/or Child-Pugh Class C, see **CONTRAINDICATIONS**)

Management of Breakthrough Pain: If episodes of breakthrough pain are encountered with appropriate adjustments of Zytram XL dose, acetaminophen, ibuprofen or tramadol may be given. If immediate release tramadol is used for breakthrough pain, the total daily dose of tramadol should not exceed 400 mg. Selection of breakthrough medication should be based on individual patient conditions. For patients whose dose has been titrated to the recommended

maintenance dose, without attainment of adequate analgesia, the total daily dose may be increased, unless precluded by side effects.

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 following abrupt discontinuation of therapy. 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 **Zytram XL** discontinuation include: panic attacks, severe anxiety, and paresthesias. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

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:

In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. 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. Seizures may be controlled with diazepam.

Tramadol is minimally eliminated from the serum by hemodialysis or hemofiltration. Therefore treatment of acute tramadol intoxication with hemodialysis or hemofiltration alone is not appropriate.

Emptying of the gastric contents is 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.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. The relationship between exposure of tramadol and M1 and efficacy has not been evaluated in the **Zytram XL** (tramadol HCl controlled release tablets) clinical studies.

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

Pharmacodynamics

The administration of naloxone only partially antagonizes tramadol's antinociceptive and analgesic effects in animals and man, indicating a contribution from non-opioid analgesic mechanisms. In animals and man the effect of tramadol is attenuated by the α_2 adrenoceptor antagonist, yohimbine, and in animals, the serotonin antagonist rianserin reduces the antinociceptive effect of tramadol. This indicates the potential for a contribution to the analgesic effect of tramadol through modulation of monaminergic inhibitory pain pathways in the dorsal horn of the spinal cord, in addition to an opioidergic effect.

Pharmacokinetics

Absorption: Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70%. The elimination half life of tramadol is around 6 hours, although this is extended to around 16 hours as a result of prolonged absorption from the **Zytram XL** tablets.

Following administration of one **Zytram XL** tablet 200 mg in the fasting state, the mean peak plasma concentration (C_{max}) was 34% (dose adjusted) that of a 100 mg dose of tramadol given as an oral solution. This was associated with a more prolonged t_{max} (median 6 hours; range 4 - 8 hours) compared with the oral solution (median 1.5 hours; range 0.75 - 4 hours). The extent of

absorption of tramadol from the **Zytram XL** tablet 200 mg was equivalent to that of the immediate release tramadol solution 100 mg, after dose adjustment. In the presence of food, the bioavailability and controlled release properties of **Zytram XL** tablets are maintained, with no evidence of dose-dumping.

In a single dose study, the dose-adjusted bioavailability of the 200 mg, 300 mg and 400 mg tablets were equivalent, confirming a linear pharmacokinetic response (in relation to both tramadol and O-desmethyltramadol) over this range of strengths.

In a steady state study, the dose adjusted bioavailability of the 150 mg and 200 mg tablets administered once-daily were equivalent. The bioavailability of all strengths of **Zytram XL** is therefore, dose-proportional. A steady-state study also confirmed that the **Zytram XL** tablet 150 mg provided an equivalent peak concentration and extent of absorption of tramadol as an immediate release capsule 50 mg administered 8-hourly.

Distribution: Tramadol has a great affinity for tissues ($V_d = 203 \pm 40$ L) and the plasma protein binding is approximately 20%.

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. Only one metabolite (mono-O-desmethyltramadol - denoted M1) is pharmacologically active. Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P-450.

Excretion: 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.

Special Populations and Conditions

Pediatrics: The safety and efficacy of **Zytram XL** has not been studied in the pediatric population. Therefore, use of **Zytram XL** tablets is not recommended in patients under 18 years of age.

Geriatrics(>65 years of 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. This difference may not be of any clinical significance.

Race: No data available.

Hepatic Insufficiency: Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in a larger area under the serum-concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). Zytram XL is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see **CONTRAINDICATIONS**)

Renal Insufficiency: Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite M1. Zytram XL is contraindicated in patients with creatinine clearances of less than 30 mL/min (see **CONTRAINDICATIONS**). The total amount of tramadol and M1 removed during a dialysis period is less than 7% of the administered dose.

Genetic Polymorphism: Not applicable.

STORAGE

Store at room temperature (15-30EC).

SPECIAL HANDLING INSTRUCTIONS

Protect from light, moisture and high humidity. Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Zytram XL 150 mg tablets are white, film coated, oval shaped tablets, plain on one side and T150 on the other. They are available in opaque plastic bottles of 50 tablets.

Zytram XL 200 mg tablets are white, film coated, oval shaped tablets, plain on one side and T200 on the other. They are available in opaque plastic bottles of 50 tablets.

Zytram XL 300 mg tablets are white, film coated, oval shaped tablets, plain on one side and T300 on the other. They are available in opaque plastic bottles of 50 tablets.

Zytram XL 400 mg tablets are white, film coated, oval shaped tablets, plain on one side and T400 on the other. They are available in opaque plastic bottles of 50 tablets.

Composition:

Active Ingredient(s): tramadol hydrochloride

Non-Medicinal Ingredients: hydrogenated vegetable oil, magnesium stearate, talc

Film Coating: hypromellose, lactose, polyethylene glycol, titanium dioxide

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

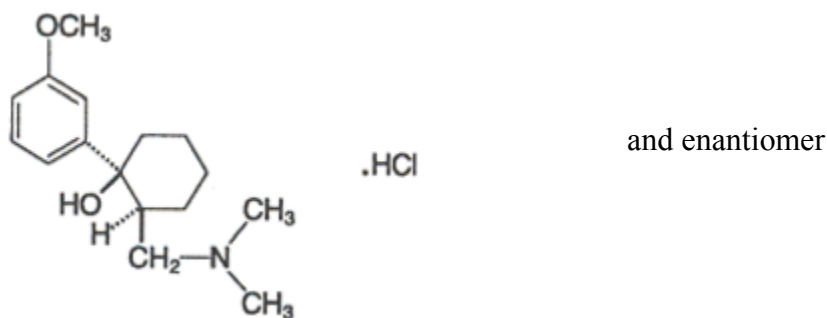
Drug Substance

Proper name: Tramadol Hydrochloride

Chemical name: (1 RS, 2 RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride

Molecular formula and molecular mass: $C_{16}H_{26}ClNO_2$ / 299.84

Structural formula:



Physicochemical properties: Tramadol is a phenyl-substituted aminomethylcyclohexanol derivative. It is a white to almost white crystalline substance, readily soluble in water and methanol.

Melting point: 180 - 184°C

CLINICAL TRIALS

Zytram XL[®] (tramadol HCl controlled release tablets) was demonstrated to be effective in the treatment of various types of chronic pain, such as osteoarthritis of hip, knee and spine and chronic low back pain. Four randomized double-blind controlled studies compared **Zytram XL** administered once daily to: sustained release diclofenac - in a parallel-group study in patients with chronic pain due to osteoarthritis (Study 1); placebo plus as required (prn) tramadol - in a crossover study in patients with chronic non-cancer pain, including osteoarthritis and low-back pain (Study 2); codeine 30mg/acetaminophen combination preparation - in a parallel-group study in patients with chronic pain due to osteoarthritis (Study 3); and placebo - in a crossover study in patients with chronic pain due to osteoarthritis (Study 4). The primary outcomes were measurements of pain intensity (VAS and/or ordinal scale) and disease-specific scales (e.g., the WOMAC Osteoarthritis Index).

Study Demographics and Trial Design

Table 1 – Study Demographics, Trial Design and Results of Study 1 (017-001)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1 (017-001)	Randomized, double-blind, parallel group, titration to effect - Zytram XL vs. SR diclofenac (Voltaren SR)	Zytram XL: 200-400 mg/day and acetaminophen PRN, oral vs. SR diclofenac (Voltaren SR): 75-150 mg/day and acetaminophen PRN, oral, 6 weeks	N=128	60.6 ± 9.5 years (Zytram XL) 64.9 ± 7.6 years (SR diclofenac)	M=42 F=86
Primary Endpoints		Associated value and statistical significance for Zytram XL vs. baseline		Associated value and statistical significance for SR diclofenac vs. baseline	
Pain intensity (100mm VAS)		Baseline 58.0 ± 17.9 Zytram XL 41.5 ± 25.5 (p = 0.0001)		Baseline 56.8 ± 23.3 SR diclofenac 39.9 ± 27.3 (p = 0.0001)	
		Mean difference in change from baseline between Zytram XL and SR diclofenac = 0.39 ± 4.89 (P = 0.7453)			
WOMAC pain subscale (5 x 100mm VAS)		Baseline 257.1 ± 98.7 Zytram XL 185.6 ± 120.8 (p = 0.0001)		Baseline 257.7 ± 116.4 SR diclofenac 174.6 ± 127.1 (p = 0.0001)	
		Mean difference in change from baseline between Zytram XL and SR diclofenac = 7.1 ± 21.7 (p = 0.9366)			

Table 2 – Study Demographics, Trial Design and Results of Study 2 (017-006)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 2 (017-006)	Randomized, double-blind, crossover, titration to effect - Zytram XL vs. placebo plus as required (PRN) IR tramadol	Zytram XL: 200-400 mg/day, oral vs. placebo plus IR tramadol PRN, oral, 8 weeks	N = 65	56.5 ± 12.7 years	M = 35 F = 30
Primary Endpoints		Associated value and statistical significance for Zytram XL		Associated value and statistical significance for placebo plus PRN tramadol	
Pain intensity (100mm VAS)		Zytram XL 29.9 ± 20.5		Placebo and PRN IR tramadol 36.1 ± 20.5	
		Zytram XL vs. placebo plus PRN IR tramadol, p = 0.0004			
Pain intensity (Ordinal Scale - 0-4)		Zytram XL 1.4 ± 0.7		Placebo and PRN IR tramadol 1.6 ± 0.6	
		Zytram XL vs. placebo plus PRN IR tramadol, p = 0.0002			

Table 3 – Study Demographics, Trial Design and Results of Study 3 (CLIN0004)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 3 (CLIN0004)	Randomized, double-blind, parallel group, titration to effect - Zytram XL vs. codeine 30mg/acetaminophen preparation	Zytram XL: 200-400 mg/day and ibuprofen rescue, oral vs. codeine 30mg/acetaminophen: 4-8 tablets/day with ibuprofen rescue, oral, 5-6 weeks	N = 259	62.4 ± 10.0 years (Zytram XL) 61.4 ± 10.4 years (codeine 30mg/acetaminophen)	M = 122 F = 137
Primary Endpoints		Zytram XL vs. codeine 30mg/acetaminophen preparation comparison			
Pain intensity (100mm VAS)					
Morning VAS		Baseline Pain*	Adjusted Mean Difference	95% Confidence Interval	
		Low	-3.1	(-10.6, 4.4)	
		Medium	1.6	(-4.2, 7.4)	
		High	6.1	(-1.3, 13.5)	
Evening VAS		Not available	-2.8	(-8.8, 3.2)	

* Treatments were compared based on reductions from baseline in three baseline pain intensity categories (low - 25% percentile, medium – 50% percentile, high – 75% percentile)

Table 4 – Study Demographics, Trial Design and Results of Study 4 (017-009)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 4 (017-009)	Randomized, double-blind, crossover, titration to effect - Zytram XL vs. placebo	Zytram XL : 150-400 mg/day and acetaminophen rescue, oral vs. placebo and acetaminophen rescue, oral, 8 weeks	N = 100	61.5 ± 10.3 years	M = 45 F = 55
Primary Endpoints		Associated value and statistical significance for Zytram XL		Associated value and statistical significance for Placebo	
Pain intensity (100mm VAS)		Baseline 50.8 ± 17.3 Zytram XL 37.4 ± 23.9 (p = 0.0001)		Baseline 50.8 ± 17.3 Placebo 45.1 ± 24.3 (p = 0.0244)	
		Zytram XL vs. placebo, p = 0.0009			
Pain intensity (Ordinal Scale - 0-4)		Baseline 2.2 ± 0.5 Zytram XL 1.7 ± 0.8 (p = 0.0001)		Baseline 2.2 ± 0.5 Placebo 1.9 ± 0.8 (p = 0.0003)	
		Zytram XL vs. placebo, p = 0.0060			
WOMAC pain subscale (5 x 100mm VAS)		Baseline 288.3 ± 78.2 Zytram XL 189.0 ± 105.0 (p = 0.0001)		Baseline 288.3 ± 78.2 Placebo 230.0 ± 115.4 (p = 0.0001)	
		Zytram XL vs. placebo, p = 0.0007			

DETAILED PHARMACOLOGY

Tramadol is a centrally acting analgesic, but is atypical in having at least two complementary mechanisms of action. It is an agonist at mu-, delta- and kappa-opioid receptors, with greater affinity for the mu-receptor. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal re-uptake of norepinephrine and serotonin, which are thought to result in activation of inhibitory pain pathways in the dorsal horn of the spinal cord. As a result, tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone. It is also antagonized by α_2 adrenoceptor antagonists.

The opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite (M1) to the mu opioid receptor. The affinity of tramadol for the mu receptor is 10 times less than codeine, 200 times less than

O-desmethyl tramadol, and 6,000 times less than morphine. The affinity of tramadol for delta and kappa opioid receptors is 20-25 times less than to mu receptors. The (+) enantiomer has 20 times greater affinity for the mu opioid receptor than the (-) enantiomer.

Tramadol inhibits the neuronal re-uptake of serotonin and also increases its release through a pre-synaptic mechanism. The (+) enantiomer is more potent than the (-) enantiomer in inhibiting serotonin reuptake. Conversely, the (-) enantiomer is more potent than the (+) enantiomer in inhibiting norepinephrine reuptake, and also increases norepinephrine release through stimulation of a pre-synaptic autoreceptor.

Both enantiomers have anti-nociceptive effects in animals and analgesic effects in humans, and the interaction between the two enantiomers is synergistic. However, for adverse effects, the interaction is less than additive (rotarod performance), additive (colonic motility) or antagonistic (cardiovascular and respiratory endpoints). Effects on gastrointestinal motility and respiration are less than with morphine, consistent with clinical observations of less constipation and respiratory depression at recommended doses.

TOXICOLOGY

After a single oral administration in mice, rats, guinea pigs, rabbits and dogs, the LD₅₀ of tramadol was 228-850 mg/kg; after s.c. injection in mice, rats and guinea pigs the LD₅₀ range was 200-286 mg/kg; after i.m. injection in rabbits and dogs, the LD₅₀ was 75-225 mg/kg; and after i.v. injection in mice, rabbits and dogs, the LD₅₀ was 45-68 mg/kg.

Clinical, hematological, clinical chemistry and histological investigations revealed no drug-related changes following repeated oral and parenteral administration for 6 and 26 weeks to rats and dogs, as well as oral administration for 12 months to dogs. Only with doses far above those used in therapy, changes in general behaviour and CNS effects, such as weight loss (probably due to reduced food intake), decreased grooming activity, restlessness, salivation and convulsions were observed.

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. Tramadol has been shown to be embryotoxic (delayed ossification) 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 those dose levels. No harm to the fetus due to tramadol was observed at doses that were not maternally toxic.

The drug had no mutagenic effect in either the micro-nucleus test, which was carried out with mice, rats and hamsters administered two single oral and parenteral doses, or in the dominant-lethal test, in which mice were administered single and repeated oral and parenteral doses.

In carcinogenicity studies using tramadol, survival analysis did not show any statistically significant positive linear trend or differences in mortality among the placebo and tramadol treatment groups.

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PART III: CONSUMER INFORMATION

^{Pr}Zytram XL[®]
Tramadol Hydrochloride
Controlled Release Tablets

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

ABOUT THIS MEDICATION

What the medication is used for:

Zytram XL is an oral tablet that slowly releases tramadol (an opioid analgesic) over a 24 hour period to manage moderate or moderately severe pain that is expected to persist for several days or more.

What it does:

Tramadol is a medicine used to treat moderate or moderately severe pain and should 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:

Zytram XL should not be used if:

- Your doctor did not prescribe it for you;
- You are allergic to tramadol, opioids or any other ingredient in the tablets;
- 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 medications (e.g., Nardil[®], Parnate[®]);
- You have kidney or liver disease.

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

Individuals under 18 years of age should not take **Zytram XL** tablets.

Use of **Zytram XL** tablets in pregnancy women is not recommended. It is not clear what effects the medication would have on the fetus.

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

Like some other pain relievers, **Zytram XL** may be habit-forming. Tell your doctor and pharmacist if you have a history of substance abuse or addiction.

What the medicinal ingredient is:

Tramadol Hydrochloride

What the nonmedicinal ingredients are:

hydrogenated vegetable oil, hypromellose, lactose, magnesium stearate, polyethylene glycol, talc, titanium dioxide (E171).

What dosage forms it comes in:

Controlled-release tablets: 150mg, 200mg, 300mg and 400mg. **Zytram XL** tablets are white, plain on one side and have a T with the mg strength on the other (i.e., T150, T200, T300, T400).

WARNINGS AND PRECAUTIONS

BEFORE you use **Zytram XL**, talk to your doctor or pharmacist if you have, or had in the past any other medical conditions (any liver, kidney or abdominal problems), are pregnant or plan to become pregnant, are breast-feeding, and if you are taking any other medications.

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 **Zytram XL**.

You should take the following precautions while taking **Zytram XL** tablets:

- You must not consume alcohol while taking **Zytram XL**, as it may increase the chance of experiencing dangerous side effects;
- Driving or other tasks requiring full alertness should not be attempted until you are sure that taking **Zytram XL** does not make you drowsy;
- 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

Drugs that may interact with **Zytram XL** 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 re-uptake inhibitors (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.

PROPER USE OF THIS MEDICATION

Zytram XL tablets should be swallowed whole and should not be broken, 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.

Usual dose:

Take the dose prescribed by your doctor. **Zytram XL** tablets should be taken regularly every 24 hour (with 4 to 6 oz. of water) to prevent pain all day and night

Zytram XL tablets may be taken with or without food.

If your pain worsens, making you uncomfortable, contact your doctor - she/he may decide that it is necessary to adjust your daily dosage of **Zytram XL**. **You should not take more than the maximum recommended dose of 400 mg of ZYTRAM XL per day.** Exceeding this recommendation can result in respiratory depression (shallow, slow breathing), seizures, coma, heart stoppage and death.

Your dose of **Zytram XL** 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 **Zytram XL**.

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 **Zytram XL** 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 **ZYTRAM XL**, call your doctor and/or your local emergency number 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 **Zytram XL**, contact your doctor immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects you may experience are constipation, dizziness, drowsiness, headache, nausea, and vomiting. Slower titration – a 7 day as compared to a 2 day schedule, 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 **Zytram XL**. Tell your doctor about these problems if they arise.

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, such as a tight chest, 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 Zytram XL, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15-30°C). Protect from moisture and high humidity.

Keep **Zytram XL** 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.

Keep **Zytram XL** out of the reach of children. Accidental overdose by a child is dangerous and may result in death.

REPORTING SUSPECTED SIDE EFFECTS

NOTE: THIS IS NOT AN EMERGENCY NUMBER

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

By toll-free telephone: 866-234-2345

By toll-free fax: 866-678-6789

On-line: www.healthcanada.gc.ca/medeffect

By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:

Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

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

MORE INFORMATION

*This leaflet summarized important information about Zytram XL.
If you would like more information, talk with your doctor and/or
pharmacist.*

<http://www.purdue.ca/products>

or by contacting the manufacturer, Purdue Pharma, at:
1-800-387-5349.

This leaflet was prepared by Purdue Pharma

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