

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrZytram XL<sup>®</sup>**

Tramadol Hydrochloride

Controlled Release Tablets – 75, 100, 150, 200, 300 and 400 mg

Purdue Pharma Standard

Opioid Analgesic

Purdue Pharma  
575 Granite Court  
Pickering, ON  
L1W 3W8

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**Pr Zytram XL®**  
Tramadol Hydrochloride Controlled Release (CR) Tablets

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
Oral	Controlled release tablets / 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg	FD&C Blue No. 2 (75 mg only), hydrogenated vegetable oil, hypromellose, iron oxide (75 mg only), lactose, magnesium stearate, polyethylene glycol, talc, titanium dioxide

**INDICATIONS AND CLINICAL USE**

**Adults**

**Zytram XL®** (tramadol hydrochloride 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)**

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Healthy elderly subjects aged 65 to 75 years administered tramadol have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. **ZYTRAM XL** 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 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 or other opioids, or to any ingredient in the formulation
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type)
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- Severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C)
- Patients with mild pain that can be managed with other pain medications
- The management of perioperative pain
- Patients with acute or severe bronchial asthma, chronic obstructive airway, and status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale
- Patients with acute alcoholism, delirium tremens, and convulsive disorders
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy)
- Women who are breastfeeding, pregnant, or during labour and delivery
- Pediatric patients less than 18 years of age who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome
- Pediatric patients less than 12 years of age

## WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

#### Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with extended-release opioid formulations, Zytram XL<sup>®</sup> should only be used in patients for whom alternative treatment options are ineffective, not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (see DOSAGE AND ADMINISTRATION).

#### Addiction, Abuse, and Misuse

Zytram XL (tramadol hydrochloride controlled release tablets) poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Zytram XL, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Zytram XL should be stored securely to avoid theft or misuse.

#### Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Zytram XL tablets. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Zytram XL or following a dose increase.

Zytram XL must be swallowed whole; cutting, breaking, crushing, chewing, or dissolving Zytram XL tablets can cause rapid release and absorption of a potentially fatal dose of tramadol (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

#### Accidental Exposure

Accidental ingestion of even one dose of Zytram XL, especially by children, can result in a fatal overdose of tramadol (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

#### Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of Zytram XL during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

#### Interaction with Alcohol

The co-ingestion of alcohol with Zytram XL may result in increased plasma levels and a potentially fatal overdose of tramadol (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

### **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of Zytram XL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

### **General**

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

Patients should be instructed not to give Zytram XL to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Zytram XL should be stored securely to avoid theft or misuse.

Zytram XL should only be prescribed by healthcare professionals who are knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Zytram XL, as it may increase the chance of experiencing dangerous side effects, including death.

Hyperalgesia that will not respond to a further dose increase of oxycodone can occur at particularly high doses. An oxycodone dose reduction or change in opioid may be required.

### **Addiction, Abuse and Misuse**

Like all opioids, Zytram XL is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Zytram XL should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Zytram XL, should be used with particular care in patients with a history of alcohol and illicit/ prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Zytram XL is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

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.

### **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**).

### **Cardiovascular**

Tramadol administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of **Zytram XL**.

The use of **Zytram XL** in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

**QTc Interval Prolongation:** The effect of tramadol on the QT/QTc interval were evaluated in a dedicated randomized, double-blind, 4-way crossover, placebo- and positive-controlled, multiple dose ECG study in healthy subjects (N=62). The study involved administration of tramadol at a supra-therapeutic dose of 100 mg every 6 h on days 1-3 (400 mg/day), with a single 100 mg dose on day 4, or 150 mg every 6 h (600 mg/day) on days 1-3, with a single 150 mg dose on day 4. The maximum placebo-adjusted mean change from baseline in the QTcF interval was 5.5 ms (90% CI 3.2, 7.8) in the 400 mg/day treatment arm and 6.5 ms (90% CI 4.1, 8.8) in the 600 mg/day mg treatment arm, both occurring at the 8h time point (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). Both treatment groups were within the 10 ms threshold for QT prolongation. Post-marketing experience with the use of tramadol containing products included rare reports of QT prolongation reported with an overdose (see **ADVERSE REACTIONS, Post-Marketing Reports with Tramadol; DRUG INTERACTIONS, QTc Interval-Prolonging Drugs; OVERDOSAGE**).

Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope,

or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering **Zytram XL** to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following:

- female gender,
- age 65 years or older,
- baseline prolongation of the QT/QTc interval,
- presence of pathological genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes,
- family history of sudden cardiac death at <50 years,
- cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease),
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation),
- electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia);
- bradycardia (<50 beats per minute),
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma),
- nutritional deficits (e.g., eating disorders, extreme diets),
- diabetes mellitus,
- autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

### **Dependence/Tolerance**

As with other opioids, tolerance and physical dependence may develop upon repeated administration of **Zytram XL** and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be

associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

#### **“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 Drug and Alcohol Addiction**

**Zytram XL** is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to **Zytram XL** unless used under extreme caution and awareness.

#### **Endocrine**

**Adrenal Insufficiency:** Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

#### **Gastrointestinal**

Tramadol and other morphine-like opioids have been shown to decrease bowel motility. Tramadol may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

#### **Neonatal Opioid Withdrawal Syndrome (NOWS)**

Prolonged maternal use of opioid during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of **Zytram XL** is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

### **Neurologic**

**Interactions with CNS Depressants (including benzodiazepines and alcohol):** Tramadol hydrochloride controlled release tablets should be used with caution and in reduced dosages during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when **Zytram XL** is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

**Zytram XL** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS, ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

**Serotonin Syndrome:** **Zytram XL** could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. **Zytram XL** should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

**Head Injury:** The respiratory depressant effects of tramadol, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, tramadol may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, tramadol must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

### **Respiratory**

**Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Tramadol should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of **Zytram XL**, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with **Zytram XL** and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of **Zytram XL** are essential. Overestimating the **Zytram XL** dose when converting patients from another opioid product can result in fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups and **DOSAGE AND ADMINISTRATION****).

**Cytochromes P450 (CYP 2D6) Ultra-Rapid Metabolism:** Some individuals may be CYP2D6 ultra-rapid metabolizers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolite O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression (see **Special Populations, Nursing Women; DRUG INTERACTIONS, Overview**). The prevalence of this CYP2D6 phenotype varies widely in the population (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Race**).

**Use in Patients with Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with **Zytram XL**, as in these patients, even usual therapeutic doses of **Zytram XL** may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of **Zytram XL** is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

### **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.

### **Perioperative Considerations**

**Zytram XL** is contraindicated for perioperative pain relief. **Zytram XL** is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with **Zytram XL** for at least 48 hours before the operation and **Zytram XL** should not be used in the immediate post-operative period and until the patient is ambulatory and gastrointestinal function is normal. If **Zytram XL** is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated (see **Withdrawal Symptoms**).

The administration of analgesics in the perioperative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Tramadol may decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving tramadol. Standard supportive therapy should be implemented.

**Zytram XL** should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

### **Psychomotor Impairment**

**Zytram XL** may impair the mental and/or physical abilities needed for potentially hazardous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly.

Patients should also be cautioned about the combined effects of tramadol with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

### **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) or serotonin-norepinephrine reuptake inhibitors (SNRIs),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, mirtazapine), or
- Opioids.

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

- MAO inhibitors (see **CONTRAINDICATIONS**),
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of seizures 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). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons and used with extreme caution. In tramadol overdose, naloxone administration may increase the risk of seizure.

### **Serotonin Syndrome Risk**

The development of a potentially life-threatening Serotonin Syndrome may occur with use of tramadol products, including **Zytram XL**, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs and triptans, with drugs which impair metabolism of serotonin (including MAOIs), and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**). This may occur within the recommended dose.

Serotonin Syndrome is likely when one of the following is observed:

- spontaneous clonus,
- inducible or ocular clonus with agitation or diaphoresis,
- tremor and hyperreflexia,
- hypertonia and body temperature  $>38^{\circ}\text{C}$  and inducible or ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement; treatment depends on the type and severity of the symptoms. As Serotonin Syndrome may result in a potentially life-threatening condition, treatment with **Zytram XL** should be discontinued if these events occur and supportive symptomatic treatment should be initiated.

### **Carcinogenesis and Mutagenesis**

See animal data in **TOXICOLOGY** section.

### **Patient Counselling Information**

A patient information sheet should be provided to patients when **Zytram XL** tablets are dispensed to them.

Patients receiving **Zytram XL** should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.
2. Patients should be advised that **Zytram XL** contains tramadol, an opioid pain medicine.
3. Patients should be advised that **Zytram XL** should only be taken as directed. The dose of **Zytram XL** should not be adjusted without consulting a physician.
4. **Zytram XL** should be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal tramadol overdose.
5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

6. Patients should not combine **Zytram XL** with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
7. Patients should be advised that serious anaphylactoid reactions have rarely been reported, however patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol.
8. Patients should be advised that **Zytram XL** may increase the risk of seizures, particularly when taken above the recommended dose range or in combination with SSRIs, tricyclic antidepressants or other tricyclic compounds or with other opioids.
9. Patients should be informed that **Zytram XL** may increase the risk of Serotonin Syndrome with concomitant use of serotonergic drugs (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.
10. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with **Zytram XL**.
11. Patients should be advised that if they have been receiving treatment with **Zytram XL** and cessation of therapy is indicated, it may be appropriate to taper **Zytram XL** dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
12. Patients should be advised of the most common adverse reactions that may occur while taking **Zytram XL**: constipation, dizziness, headache, nausea, somnolence and vomiting.
13. Patients should be advised that **Zytram XL** may cause drowsiness, dizziness, or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on **Zytram XL** or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of **Zytram XL**.
14. Patients should be advised that **Zytram XL** is a potential drug of abuse. They should protect it from theft or misuse.
15. Patients should be advised that **Zytram XL** should never be given to anyone other than the individual for whom it was prescribed.
16. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with **Zytram XL**. Women who are breastfeeding or pregnant should not use **Zytram XL**.
17. Patients should be advised that they may pass empty matrix tablet remnants in the stool, or via colostomy, and that this should not be a concern since the analgesic medication, tramadol, has already been released.

### **Sexual Function / Reproduction**

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Marketing Experience**).

### **Special Populations**

**Special Risk Groups:** Tramadol should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

**Pregnant Women:** Studies in humans have not been conducted. **Zytram XL** crosses the placental barrier and is contraindicated in pregnant women.

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS), ADVERSE REACTIONS**). Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during post-marketing reports with tramadol hydrochloride immediate-release products. Use of **Zytram XL** is contraindicated in pregnant women (see **CONTRAINDICATIONS**). The effect of tramadol, if any, on the later growth, development and functional maturation of the child is unknown.

**Labour, Delivery and Nursing Women:** Since opioids can cross the placental barrier and are excreted in breast milk, **Zytram XL** is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if **Zytram XL** is used in this population.

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

Some women are CYP2D6 ultra-rapid metabolizers of tramadol, which may lead to dangerously higher-than-expected serum levels of M1 that could pass to their breast-fed infants. Therefore, maternal use of tramadol can lead to serious adverse reactions, including death in nursing infants (see **WARNINGS AND PRECAUTIONS, Respiratory**).

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 breastfeeding.

**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. Further, adolescent patients (12 to 18 years old) who are obese or have conditions such as obstructive sleep apnea or severe lung disease may be at increased risk of serious breathing problems; the use of **Zytram XL** is not recommended in these pediatrics patients.

**Geriatrics (>65 years of age):** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, 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 (see **DOSAGE AND ADMINISTRATION**).

**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.

**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.

### **Monitoring and Laboratory Tests**

Not applicable.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Adverse effects of **Zytram XL**<sup>®</sup> (tramadol hydrochloride controlled release tablets) are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The pre-marketing development program for **Zytram XL** (tramadol hydrochloride controlled release tablets) included exposure to a total of 1,213 participants in seven randomized, double-blind controlled clinical trials (n = 1,028) 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%)**

	<b>Number of Patients</b>	<b>% of Patients n = 1,213</b>
<b>Body as a Whole</b>		
Headache	132	10.9
Asthenia	93	7.7
Hyperhidrosis	69	5.7
Pain	26	2.1
<b>Central Nervous System</b>		
Dizziness	214	17.6
Somnolence	191	15.7
Depression	12	1.0
Insomnia	24	2.0
Tremor	13	1.1
Vasodilation	24	2.0
<b>Digestive System</b>		
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
<b>Respiratory System</b>		
Cough increased	11	1.0
Pharyngitis	17	1.4
<b>Skin and Appendages</b>		
Pruritus	27	2.2

**Sedation:** Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

**Nausea and Vomiting:** Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

**Constipation:** Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in **Zytram XL** clinical trials, whether related or not to tramadol.

### **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.

<u>Digestive:</u>	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.
<u>Endocrine:</u>	abnormal ejaculation, impotence, libido decreased.
<u>Hemolytic &amp; Lymphatic:</u>	hemolytic anemia, liver function test abnormal.
<u>Metabolic &amp; Nutritional:</u>	alkaline phosphatase increased, hypercholesteremia, hyperglycemia, hyperlipemia, peripheral edema, hepatic enzymes increased.
<u>Musculoskeletal:</u>	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, confusional state, depersonalization, affect lability, euphoric mood, hallucinations, hyperesthesia, hypertonia, anosmia or hyposmia, 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, visual impairment.
<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, angioedema and urticaria), bradycardia, cognitive disorders, seizures, decreased activity, drug dependence, drug withdrawal (including agitation, anxiety, gastrointestinal symptoms, hyperkinesia, insomnia, nervousness, tremor), hypotension, micturition disorder, psychomotor hyperactivity, respiratory depression and sensory disturbance.

Cases of hypoglycemia have been reported in patients taking tramadol, mostly in patients with pre-disposing risk factors, including diabetes, elderly and renal insufficiency. Caution should be exercised when prescribing tramadol to diabetic patients. More frequent monitoring of blood glucose levels may be appropriate.

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.

Electrocardiogram QT prolonged, ventricular fibrillation, and ventricular tachycardia have been reported during post-market use.

Neonatal opioid withdrawal syndrome has resulted from prolonged use of tramadol.

### **Post-Marketing Experience**

**Androgen deficiency:** Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

## 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.

**Interaction with Benzodiazepines and Other CNS Depressants:** Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). **Zytram XL** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

### **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), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants (TCAs), anti-psychotics and other seizure threshold lowering drugs (i.e., bupropion, mirtazapine, tetrahydrocannabinol) to cause seizures (see **WARNINGS AND PRECAUTIONS**).

#### ***Serotonergic Agents***

The development of a potentially life-threatening Serotonin Syndrome may occur with use of tramadol products, including **Zytram XL**, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium or St. John's Wort, with drugs which impair metabolism of serotonin (including MAOIs), and with drugs which may impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). If concomitant treatment of **Zytram XL** with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

### ***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 or exacerbate adverse drug reactions of tramadol.

### ***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**<sup>®</sup> (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.

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors such as quinidine, fluoxetine, paroxetine, amitriptyline (CYP2D6 inhibitors), ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol, increasing the risk for serious adverse events including seizures, serotonin syndrome, and QTc interval prolongation, potentially resulting in cardiac arrhythmias.

### **QTc Interval-Prolonging Drugs**

The concomitant use of **Zytram XL** with QTc interval-prolonging drugs should be avoided. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class IC antiarrhythmics (e.g., flecainide, propafenone)

- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic
- antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-hydroxytryptamine (5-HT)<sub>3</sub> receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

### **Drugs that Affect Electrolytes**

The use of **Zytram XL** with drugs that can decrease electrolyte levels should be avoided to the extent possible. Drugs that can decrease electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids
- proton pump inhibitors

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or decrease electrolytes, as well as for older drugs for which these effects have recently been established. (See **WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Post-Marketing Reports with Tramadol; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

### ***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 (international normalized ratio/INR), 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, care should be taken when commencing treatment with tramadol in patients on anticoagulants. 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.

**Drug-Lifestyle Interactions**

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box**).

**DOSAGE AND ADMINISTRATION**

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that a maximum daily dosage of 400 mg (66.7 morphine milligram equivalent) of **Zytram XL**<sup>®</sup> (tramadol hydrochloride controlled release tablets) not be exceeded. Each patient should be assessed for their risk prior to prescribing **Zytram XL**, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of **Zytram XL** (see **DOSAGE AND ADMINISTRATION, Adjustment or reduction of Dosage**).

**Zytram XL** should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

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

The empty matrix tablet remnants may be visible in the stool, or via colostomy.

### **Dosing Considerations**

**Zytram XL** should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Perioperative Considerations**).

**Zytram XL** may be taken with or without food, with a glass of water.

**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 not indicated for rectal administration.

### **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 150 mg.

The 75 mg and 100 mg tablets allow for smaller dose increases and can be used for initiation, titration or adjustments of 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.

**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 every 24h.

**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.

**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 patients with renal and/or hepatic insufficiency. 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**).

**Geriatrics (> 65 years old):** Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. It is recommended that a reduced daily dose should be considered as an alternative to a prolongation in dosage interval. **Zytram XL** should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

**Use with Non-Opioid Medications:** If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. **Zytram XL** can be safely used concomitantly with usual doses of other non-opioid analgesics.

**Dose Titration:** Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at regular administration of the lowest dose of controlled release tramadol (Zytram XL) which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

**Adjustment or Reduction of Dosage:** Dosage adjustments should be based on the patient's clinical response. In patients receiving **Zytram XL** it is recommended that doses be slowly titrated, with dosage adjustments generally separated by 7 days, to a dose which provides satisfactory pain relief for a full 24 hours, with acceptable side effects.

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including **Zytram XL**. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

**Management of Patients Requiring Rescue Medication:** If rescue medications are warranted for episodes of pain in the course of appropriate adjustments of **Zytram XL** dose, medications such as acetaminophen, ibuprofen or tramadol IR may be given. Fentanyl products should not be used as rescue medication in patients taking **Zytram XL**. If immediate release tramadol is used as rescue medication, the total daily dose of tramadol should not exceed 400 mg. Selection of rescue 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.

#### **Disposal**

**Zytram XL** should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. **Zytram XL** should not be used in front of children, since they may copy these actions.

**Zytram XL should never be disposed of in household trash.** Disposal via a pharmacy take back program is recommended. Unused or expired **Zytram XL** should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. **Zytram XL** should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

## OVERDOSAGE

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

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, miosis, bradycardia, hypotension, vomiting, circulatory collapse, seizures, and death. In addition, cases of QT prolongation have been reported during overdose.

### **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. Naloxone will not antagonize tramadol's inhibitory effects on serotonin reuptake and norepinephrine reuptake. 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  $\mu$ -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  $\mu$ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in  $\mu$ -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**<sup>®</sup> (tramadol hydrochloride 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  $\alpha_2$  adrenoceptor antagonist, yohimbine, and in animals, the serotonin antagonist ritanserin reduces the antinociceptive effect of tramadol. This indicates the potential for a contribution to the analgesic effect of tramadol through modulation of monoaminergic inhibitory pain pathways in the dorsal horn of the spinal cord, in addition to an opioidergic effect.

**Cardiac Electrophysiology:** In a randomized, double-blind, 4-way crossover, placebo- and positive-controlled, multiple dose ECG assessment study in healthy subjects (N=62), the following tramadol treatments were tested: A) 100 mg every 6 h on days 1-3 (400 mg/day), with a single 100 mg dose on day 4 and B) 150 mg every 6 h (600 mg/day) on days 1-3, with a single 150 mg dose on day 4. The maximum dose for Zytram XL is 300 mg/day. In both treatment arms, the maximum difference from placebo in the mean change from baseline QTcF interval occurred at the 8 h time point: 5.5 ms (90% CI 3.2, 7.8) in the 400 mg/day treatment arm and 6.5 ms (90% CI 4.1, 8.8) in the 600 mg/day mg treatment arm. Both treatment groups were within the 10 ms threshold for QT prolongation (see **WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Post-Marketing Reports with Tramadol; DRUG INTERACTIONS, QTc Interval-Prolonging Drugs; DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment; OVERDOSAGE**).

**Central Nervous System:** Tramadol produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO<sub>2</sub> tension and to electrical stimulation. Tramadol depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Tramadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce

similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

**Gastrointestinal Tract and Other Smooth Muscle:** Tramadol causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

**Cardiovascular System:** Tramadol may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

**Endocrine System:** Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

**Immune System:** *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

### **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 P450.

**Elimination:** Tramadol and its metabolites are almost completely excreted with the urine. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites.

The elimination half-life of tramadol is around 6 hours, although this is extended to around 12 to 16 hours following prolonged absorption from the controlled release tablet.

### **Special Populations and Conditions**

**Pediatrics:** The safety and efficacy of **Zytram XL** has not been studied in the pediatric population. Individuals under 18 years of age should not take **Zytram XL**.

**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:** Some patients are CYP2D6 ultra-rapid metabolizers of tramadol due to a specific genotype. These individuals convert tramadol into its active metabolite, M1, more rapidly and completely than other people leading to higher-than-expected serum M1 levels. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5% to 1% in Chinese, Japanese and Hispanics, 1% to 10% in Caucasians, 3% in African Americans, and 16% to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups (see **WARNINGS AND PRECAUTIONS**, **Respiratory** and **Special Populations, Nursing Women**).

In contrast, some patients exhibit the CYP2D6 poor metabolizer phenotype and do not convert tramadol to the active M1 metabolite sufficiently to benefit from the analgesic effect of the drug (see **DRUG INTERACTIONS, Overview**). The prevalence of this CYP2D6 phenotype is about 5% - 10% in Caucasians and 1% of Asians.

**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 hours for tramadol and 19 hours 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°C - 30°C).

## SPECIAL HANDLING INSTRUCTIONS

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

## DOSAGE FORMS, COMPOSITION AND PACKAGING

**Zytram XL** 75 mg tablets are pale grey, film-coated, round tablets, marked with a T on one side and 75 on the other. They are available in opaque plastic bottles of 60 tablets and PVC blister packages of 50 tablets.

**Zytram XL** 100 mg tablets are white, film-coated, round tablets, marked with a T on one side and 100 on the other. They are available in opaque plastic bottles of 60 tablets and PVC blister packages of 50 tablets.

**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 60 tablets and PVC blister packages 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 60 tablets and PVC blister packages 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 60 tablets and PVC blister packages 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 60 tablets and PVC blister packages of 50 tablets.

**Composition:**

Active Ingredient(s): tramadol hydrochloride

Nonmedicinal Ingredients: hydrogenated vegetable oil, hypromellose, lactose, magnesium stearate, polyethylene glycol, talc, titanium dioxide. The 75 mg tablets also contain iron oxide and FD&C Blue No. 2.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

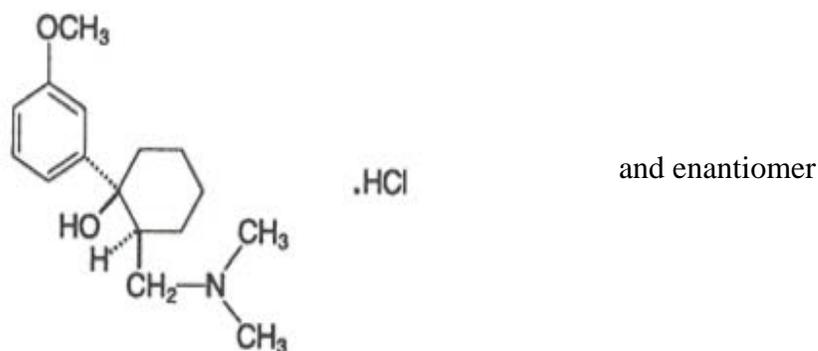
#### Drug Substance

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

**Figure 1: Structural formula - Tramadol Hydrochloride**



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°C - 184°C

## CLINICAL TRIALS

**Zytram XL**<sup>®</sup> (tramadol hydrochloride 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 30 mg/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 2: 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 - <b>Zytram XL</b> vs. SR diclofenac (Voltaren SR)	<b>Zytram XL:</b> 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 ( <b>Zytram XL</b> ) 64.9 ± 7.6 years (SR diclofenac)	M=42 F=86
<b>Primary Endpoints</b>		<b>Associated value and statistical significance for Zytram XL vs. baseline</b>		<b>Associated value and statistical significance for SR diclofenac vs. baseline</b>	
Pain intensity (100 mm VAS)		Baseline 58.0 ± 17.9 <b>Zytram XL</b> 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 <b>Zytram XL</b> and SR diclofenac = 0.39 ± 4.89 (P = 0.7453)			
WOMAC pain subscale (5 x 100 mm VAS)		Baseline 257.1 ± 98.7 <b>Zytram XL</b> 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 <b>Zytram XL</b> and SR diclofenac = 7.1 ± 21.7 (p = 0.9366)			

**Table 3: 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 - <b>Zytram XL</b> vs. placebo plus as required (PRN) IR tramadol	<b>Zytram XL:</b> 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
<b>Primary Endpoints</b>		<b>Associated value and statistical significance for Zytram XL</b>		<b>Associated value and statistical significance for placebo plus PRN tramadol</b>	
Pain intensity (100 mm VAS)		<b>Zytram XL</b> 29.9 ± 20.5		Placebo and PRN IR tramadol 36.1 ± 20.5	
		<b>Zytram XL vs. placebo plus PRN IR tramadol, p = 0.0004</b>			
Pain intensity (Ordinal Scale - 0-4)		<b>Zytram XL</b> 1.4 ± 0.7		Placebo and PRN IR tramadol 1.6 ± 0.6	
		<b>Zytram XL vs. placebo plus PRN IR tramadol, p = 0.0002</b>			

**Table 4: 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 - <b>Zytram XL</b> vs. codeine 30 mg/acetaminophen preparation	<b>Zytram XL:</b> 200-400 mg/day and ibuprofen rescue, oral vs. codeine 30 mg/acetaminophen: 4-8 tablets/day with ibuprofen rescue, oral, 5-6 weeks	N = 259	62.4 ± 10.0 years <b>(Zytram XL)</b> 61.4 ± 10.4 years (codeine 30 mg/acetaminophen)	M = 122 F = 137
<b>Primary Endpoints</b>		<b>Zytram XL vs. codeine 30 mg/acetaminophen preparation comparison</b>			
Pain intensity (100 mm 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 5: 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 - <b>Zytram XL</b> vs. placebo	<b>Zytram XL</b> : 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
<b>Primary Endpoints</b>		<b>Associated value and statistical significance for Zytram XL</b>		<b>Associated value and statistical significance for Placebo</b>	
Pain intensity (100 mm VAS)		Baseline	50.8 ± 17.3	Baseline	50.8 ± 17.3
		<b>Zytram XL</b>	37.4 ± 23.9 (p = 0.0001)	Placebo	45.1 ± 24.3 (p = 0.0244)
<b>Zytram XL vs. placebo, p = 0.0009</b>					
Pain intensity (Ordinal Scale - 0-4)		Baseline	2.2 ± 0.5	Baseline	2.2 ± 0.5
		<b>Zytram XL</b>	1.7 ± 0.8 (p = 0.0001)	Placebo	1.9 ± 0.8 (p = 0.0003)
<b>Zytram XL vs. placebo, p = 0.0060</b>					
WOMAC pain subscale (5 x 100 mm VAS)		Baseline	288.3 ± 78.2	Baseline	288.3 ± 78.2
		<b>Zytram XL</b>	189.0 ± 105.0 (p = 0.0001)	Placebo	230.0 ± 115.4 (p = 0.0001)
<b>Zytram XL vs. placebo, p = 0.0007</b>					

## DETAILED PHARMACOLOGY

### Mechanism of Action

Tramadol is a centrally acting analgesic, but is atypical in having at least two complementary mechanisms of action. It is a non-selective pure 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  $\alpha_2$  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 LD<sub>50</sub> of tramadol was 228-850 mg/kg; after s.c. injection in mice, rats and guinea pigs the LD<sub>50</sub> range was 200-286 mg/kg; after i.m. injection in rabbits and dogs, the LD<sub>50</sub> was 75-225 mg/kg; and after i.v. injection in mice, rabbits and dogs, the LD<sub>50</sub> 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.

### **Reproductive and Developmental Toxicity**

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.

### **Mutagenicity**

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.

### **Carcinogenicity**

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.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

**PrZytram XL<sup>®</sup>**  
**Tramadol Controlled Release Tablets**

Read this carefully before you start taking **Zytram XL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Zytram XL**.

**Serious Warnings and Precautions**

- **Even if you take Zytram XL as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take Zytram XL it must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking Zytram XL. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your Zytram XL. They could die from taking it. If a person has not been prescribed Zytram XL, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Zytram XL while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking Zytram XL with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

**What is Zytram XL used for?**

**Zytram XL** is a medicine used to manage your pain.

## **How does Zytram XL work?**

Zytram XL is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain. It contains tramadol, 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).

## **What are the ingredients in Zytram XL?**

Medicinal ingredient: tramadol hydrochloride

Non-medicinal ingredients:

hydrogenated vegetable oil, hypromellose, lactose, magnesium stearate, polyethylene glycol, talc, titanium dioxide. The 75 mg tablets also contain iron oxide and FD&C Blue No. 2.

## **Zytram XL comes in the following dosage forms:**

**Zytram XL** Controlled Release Tablets: 75 mg, 100 mg, 150 mg, 200 mg, 300 mg and 400 mg

## **Do not use Zytram XL if:**

- your doctor did not prescribe it for you
- you are allergic to tramadol, other opioids, or any of the other ingredients in **Zytram XL**
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have severe liver disease
- you have severe kidney disease
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline)
- you are less than 18 years old and having (or recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep
- you are less than 12 years old
- you are pregnant, planning to become pregnant, in labour or breastfeeding

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Zytram XL. Talk about any health conditions or problems you may have, including if you:**

- have alcohol or drug withdrawal or a history of illicit or prescription drug or alcohol abuse
- have had seizures (convulsions)
- have a condition that may put you at increased risk of seizures (epilepsy)
- central nervous system (CNS) infection
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have been told that you metabolize tramadol or other pain medications rapidly
- have diabetes
- you had surgery within the last 12 -24 hours
- you have a planned surgery within the next 24 hours
- have problems with your thyroid, adrenal or prostate gland
- have or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are over 65 years of age

**Other warnings you should know about:**

**Zytram XL** can decrease your blood sugar levels. Diabetic patients may need to monitor their blood sugar more often. If you notice changes, discuss this with your doctor.

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

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

**Alcohol:** You must not consume alcohol while taking **Zytram XL** 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.

**Opioid dependence and addiction:** There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

**Pregnancy, nursing, labour and delivery:** Do not use **Zytram XL** while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. **Zytram XL** can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking **Zytram XL**, it is important that you don't stop taking your

medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking **Zytram XL**. This may help avoid serious harm to your unborn baby.

**Adolescents (12 to 18 years old):** You should not use **Zytram XL** if your child:

- is overweight (obese)
- has obstructive sleep apnea (a condition where your breathing starts and stops while you sleep)
- has severe lung disease

There is a higher risk of serious breathing problems if your child takes **Zytram XL** and has any of the above conditions.

**Allergic reactions:** 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.

You may see tablets in your stools (bowel movements) or in your colostomy, when using **Zytram XL**. Do not be concerned, the medication has already been released.

**Driving and using machines:** Before you do tasks which may require special attention, you should wait until you know how you react to **Zytram XL**. **Zytram XL** can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

**Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off **Zytram XL**.

**Serotonin syndrome:** **Zytram XL** can cause serotonin syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin syndrome if you take **Zytram XL** with certain antidepressants or migraine medications.

Serotonin syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

**Sexual Function/Reproduction:** Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Zytram XL:**

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking **Zytram XL**. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take **Zytram XL** with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- herbal remedies (e.g. St. John's Wort)
- drugs used to treat migraine headaches
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- anticoagulants (blood thinners)
- anticonvulsant drugs (used to treat epilepsy)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- heart medications (e.g. digoxin, quinidine)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

## **How to take Zytram XL:**

Take **Zytram XL** tablets regularly every 24 hours, with or without food, with a full glass of water.

**Zytram XL** is not recommended for rectal administration.

**Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**

## **Usual Adult Starting Dose:**

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor. Taking higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need **Zytram XL**. Be sure to use **Zytram XL** only for the condition for which it was prescribed.

The usual starting dose of **Zytram XL** is 150 mg per day. 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.

If your pain increases or you develop any side effect as a result of taking **Zytram XL**, tell your doctor immediately.

## **Stopping your Medication:**

If you have been taking **Zytram XL** for more than a few days you should not stop taking it all of a sudden. You should check with your doctor for directions on how to slowly stop taking it. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- an unexplained fever
- weakness

- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking **Zytram XL**.

### **Refilling your Prescription for Zytram XL:**

A prescription is required from your doctor when you need **Zytram XL**. It is important that you contact your doctor about your medication supply.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

### **Overdose:**

If you think you have taken too much **Zytram XL**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness
- fits (seizures)
- irritation and discomfort in the stomach and gut
- loss of appetite
- nausea
- vomiting
- feeling unwell
- unusually pale color and sweating

Cases of abnormal electrical conduction in the heart (QT prolongation) have been reported.

### **Missed Dose:**

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in succession, talk to your doctor before restarting your medication.

### **What are possible side effects from using Zytram XL?**

These are not all the possible side effects you may feel when taking **Zytram XL**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Light headedness
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using **Zytram XL**.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
<b>RARE</b>	<b>Overdose:</b> hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
	<b>Respiratory Depression:</b> slow, shallow or weak breathing.			√
<b>RARE</b>	<b>Allergic Reaction:</b> rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	<b>Bowel Blockage (impaction):</b> abdominal pain, severe constipation, nausea			√
	<b>Withdrawal:</b> nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
	<b>Fast, Slow or Irregular Heartbeat:</b> heart palpitations.		√	
	<b>Low Blood Pressure:</b> dizziness, fainting, light-	√		

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	headedness.			
	<b>Serotonin Syndrome:</b> agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea.			√
<b>VERY RARE</b>	<b>Decreased Blood Sugar (hypoglycemia):</b> dizziness, lack of energy, drowsiness, headache, trembling, sweating.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

**3 ways to report:**

- Online at MedEffect: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 1908C  
Ottawa, ON  
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>).

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

**Storage:**

- Store at room temperature (15°C- 30°C). Keep in a dry place.
- **Keep unused or expired Zytram XL in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep Zytram XL under lock, out of sight and reach of children and pets.**

**Disposal:**

**Zytram XL should never be thrown into household trash, where children and pets may find it.** It should be returned to a pharmacy for proper disposal.

**If you want more information about Zytram XL:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.purdue.ca>, or by calling 1-800-387-4501.

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