Tramadol Hydrochloride
Siverol®

50 mg Capsule
50 mg/1 mL Solution for Injection
100 mg/2 mL Solution for Injection

Opioid Analgesic

FORMULATION

Each capsule contains:
Tramadol Hcl .... 50 mg

Each 1 mL ampule contains:
Tramadol Hcl .... 50 mg

Each 2 mL ampule contains:
Tramadol Hcl .... 100 mg

PRODUCT DESCRIPTION

Siverol 50mg Capsule: Hard gelatin capsule with a green opaque cap and an ivory opaque body

Siverol 50 mg/1 mL Solution for Injection: Clear, sterile, colorless solution, free from extraneous matter, filled in a 2 mL clear ampule with blue dot

Siverol 100 mg/2 mL Solution for Injection: Clear, sterile, colorless solution, free from extraneous matter, filled in a 2 mL clear ampule with blue dot

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Tramadol is a synthetic opioid analgesic that acts on the central nervous system. It is a pure non-selective agonist of the μ, δ, and opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal uptake of noradrenaline and enhancement of serotonin release.

PHARMACOKINETICS
After oral administration of a single 50 mg capsule, tramadol is rapidly and almost completely absorbed with a mean absorption delay of approximately 30 minutes. Food does not significantly affect the rate or extent of absorption. The absorption half-life is 23 ± 11 minutes.

Tramadol has a high tissue affinity with a volume of distribution of 2 to 3 L/kg in young adults. The volume of distribution is reduced by about 25% in those over 75 years old. Plasma protein binding is about 20% and is independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

After oral administration of two 50 mg capsules, the mean absolute bioavailability is 68 to 72%, while the mean absolute bioavailability of a single oral 100 mg dose is approximately 75%. Peak serum level (C_{max}) of tramadol is reached approximately two hours after oral administration. C_{max} is approximately 280 ng/mL after oral administration (100 mg), while the mean serum concentration after intravenous (IV) administration is 410 ng/mL (1.46 times higher). After repeated oral administration of 50 mg and 100 mg tramadol capsules every six hours, steady state is reached 30 to 36 hours after the first administration and bioavailability is greater than 90%. After intramuscular (IM) injection of 50 mg tramadol, bioavailability is approximately 100% and peak serum level is attained after 45 minutes. The peak concentrations of M1 metabolite (major metabolite) occur three hours after tramadol administration.

Tramadol crosses the placental and blood-brain barriers. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor. The cumulative excretion in breastmilk within 16 hours post-dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg (0.02% of the maternal dose) of M1 after a single 100 mg IV dose of tramadol.

Tramadol is extensively metabolized in the liver. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation. Only M1 is pharmacologically active. Production of M1 is dependent on the cytochrome P (CYP) 2D6 isoenzyme of CYP450. Patients who metabolize drugs poorly via CYP2D6 may obtain reduced benefit from tramadol, due to reduced formation of M1. *N*-demethylation is catalyzed by the CYP3A4 isoenzyme of CYP450. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentrations of tramadol or its active metabolite.

Tramadol and its metabolites are excreted mainly by the kidneys with a cumulative renal excretion (tramadol and metabolites) of approximately 95%. In young adults, approximately 15 to 19% of an administered dose is excreted in the urine as unchanged drug. Biliary excretion is of little importance. The half-life of tramadol is five to seven hours and the half-life of M1 is six to eight hours. Total clearance is approximately 430 to 610 mL/min.

Special Populations:

Renal Impairment: Elimination of tramadol and M1 is diminished in patients with renal impairment. In patients with renal failure (creatinine clearance < 5 mL/min), the half-life of tramadol was 11 hours and that of M1 was 17 hours.

Hepatic Impairment: Elimination of tramadol and M1 is diminished in patients with hepatic impairment, the mean half-life of tramadol was 13 hours and the mean half-life of M1 was 19 hours.

Elderly: In the elderly (>75 years old), tramadol's volume of distribution is decreased by 25% and clearance is decreased by 40%. As a result, tramadol's C_{max} and total exposure are increased by 30% and 50%, respectively. However, the half-life of tramadol is only slightly prolonged by 15%.

INDICATIONS
> Relief of moderate to severe pain

DOSAGE AND MODE OF ADMINISTRATION
Like any other analgesic drug, the dosing of tramadol should be adjusted according to the severity of pain and patient's clinical response.

The lowest effective analgesic dose should be given.

Strict aseptic technique should be observed when drawing up the contents of tramadol ampule. If injection ampules become contaminated, they have the potential to become a source of infection to patients.

Adults and children over 12 years old:

DOSAGE FORM	PAIN SEVERITY	RECOMMENDED DOSE
FOR ORAL ADMINISTRATION: Tramadol 50 mg Capsule	Moderate pain	• Initial Dose: Orally, 50 mg (1 capsule) administered two to three times daily. • May be increased to 100 mg (2 capsules) two to three times daily.
	Moderate to Severe pain	• Orally, 50 mg to 100 mg (1 to 2 capsules) as needed, every four to six hours. • The 100 mg dose is usually more effective as the initial dose for more severe pain. • **Maximum Dose:** 400 mg/day
FOR PARENTERAL ADMINISTRATION: Intravenous (IV) or Intramuscular (IM) injection **Tramadol 50 mg/1 mL Solution for Injection or Tramadol 100 mg/2 mL Solution for Injection**	Postoperative pain	• Initial bolus of 100 mg should be administered. • During the 60 minutes after the bolus, additional doses of 50 mg may be given every 10 to 20 minutes up to a total dose of 250 mg (including the bolus dose). • Subsequent doses of 50 mg or 100 mg every 4 to 6 hours may be given, up to a total daily dose of 600 mg. A total parenteral daily dose of 600 mg should not be exceeded except in special circumstances.
	Less severe pain	• 50 mg or 100 mg administered every 4 to 6 hours not to exceed 400 mg/day.
Intravenous injection should be given slowly over 2 to 3 minutes.		
Or, as prescribed by a physician		

Special Populations:

Patients with Renal Impairment/Renal Dialysis
- Impaired renal function results in a decreased rate and extent of excretion of tramadol and M1. The usual initial adult doses should be employed, but the dosage interval should be adjusted.
- *Creatinine clearance <30 mL/min:* Dose interval should be increased to 12 hours.
- Patients on hemodialysis can receive their regular dose on the day of dialysis since only seven percent of an administered dose is removed by hemodialysis.
- Tramadol is removed very slowly by hemodialysis or hemofiltration and therefore post-dialysis dosing to maintain analgesia is usually unnecessary.

Patients with Hepatic Impairment
- The elimination of tramadol may be prolonged. Depending on the severity of the impairment and individual clinical response, the usual dosage should be divided in two or the dosage interval should be extended to 12 hours.

Elderly patients
- Changes in renal and/or hepatic function in the elderly may require dose adjustment. Daily doses of 300 mg are not recommended in patients over 75 years old.

CONTRAINDICATIONS
- Hypersensitivity to tramadol, opioids or to any component in the product
- Acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drug (See ***Interactions with Other Medicaments***)
- Patients on monoamine oxidase inhibitor (MAOI) therapy or if patients have taken such medications within the last 14 days before treatment with tramadol. (See ***Interactions with Other Medicaments***)
- Severe hepatic or renal impairment
- Severely impaired kidney function (creatinine clearance < 10 mL/min)
- Severe respiratory impairment (e.g., acute or severe bronchial asthma) in an unmonitored setting or in the absence of resuscitative equipment
- Suspected or known mechanical gastrointestinal (GI) obstruction (e.g., bowel obstruction or strictures); or any diseases/conditions affecting bowel transit (e.g., ileus of any type); or in patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- Children who are younger than 12 years old and to patients younger than 18 years old who have tonsillectomy and/or adenoidectomy
- Significant respiratory depression
- Patients suffering from uncontrolled epilepsy, or epilepsy not adequately controlled by treatment
- Tramadol must not be used for narcotic withdrawal treatment.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse
The use of tramadol HCl exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. The patient's risk should be assessed prior to prescribing tramadol, and the development of related behaviors and conditions should be monitored regularly. (See ***Warnings and Precautions***)

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with the use of tramadol. Close monitoring for respiratory depression should be performed, especially during initiation of tramadol and following a dose increase. (See ***Warnings and Precautions***)

Accidental Ingestion
Accidental ingestion of even one tramadol dose, particularly by children, can result in respiratory depression and death. Patients should be instructed that medicines containing tramadol should be securely stored. Unused tramadol-containing medicines should also be disposed accordingly.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of tramadol during pregnancy may lead to opioid withdrawal in the neonate. Neonatal opioid may be fatal if not immediately recognized and treated. It also requires management according to protocols developed by neonatology experts. Signs of neonatal opioid withdrawal syndrome should be observed in newborns and should be managed accordingly. If the prolonged use of opioid is necessary during pregnancy, the patient should be advised of the risk of neonatal opioid withdrawal syndrome and guarantee that the appropriate treatment will be available.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The concomitant use or discontinuation of cytochrome (CYP) P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol produces complex effects. Therefore, careful consideration on the effects of the concomitant use of these agents on tramadol (a weak serotonin and norepinephrine reuptake inhibitor and μ-opioid agonist) and M1 (which is more potent than tramadol in μ-opioid receptor binding) is required. (See ***Warnings and Precautions***)

Risks from Concomitant Use with Benzodiazepines or Other Central Nervous System (CNS) Depressants
The concurrent use of opioids with CNS depressants (e.g., benzodiazepines, alcohol) can result in respiratory depression, coma, and death. (See ***Warnings and Precautions***)
- The concomitant prescribing of tramadol with benzodiazepines or other CNS depressants should be reserved for use in patients for whom alternative treatment options are inadequate.
- Treatment should be limited to the minimum effective dosages and durations.
- Monitor patients for signs and symptoms of respiratory depression and sedation.

Addiction, Abuse, and Misuse
As an opioid analgesic, the use of tramadol HCl is associated with the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Addiction may occur even if tramadol is appropriately prescribed at recommended dosages and if it is abused or misused.

The patient's risk should be assessed prior to prescribing tramadol, and the development of related behaviors and conditions should be monitored regularly. Patients with a personal or family history of substance abuse (such as drug or alcohol abuse or addiction) or mental illness (e.g., major depression) have an increased risk for addiction. However, these potential risks should not interfere with the proper pain management on any patient. Though tramadol may be prescribed in high-risk patients, it may require intensive counseling about the risks and proper use of tramadol, together with intensive monitoring for signs of addiction, abuse, and misuse.

Strategies to reduce the risk of addiction (e.g., prescribing the drug in the smallest appropriate dose; advising the patient on the proper disposal of the unused drug) should be considered when prescribing or dispensing tramadol.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with the use of tramadol. If not immediately diagnosed and treated, respiratory depression may lead to respiratory arrest and death. The sedating effects of opioids can be exacerbated by the carbon dioxide retention from opioid-induced respiratory depression. Management of respiratory depression (which may include close observation, supportive measures, and use of opioid antagonists) should be performed, depending on the clinical status of the patient. Patients with impending respiratory depression should be immediately brought to an emergency room with facilities for respiratory/ventilatory support.

Although serious, life-threatening, or fatal respiratory depression can occur at any time with the use of tramadol, the risk is greatest during the initiation of tramadol therapy or following a dose increase. Thus, close monitoring for respiratory depression should be performed, especially within the first 24 to 72 hours of treatment initiation and following dosage increases.

Proper dosing and titration of tramadol are necessary to reduce the risk of respiratory depression. Overestimation of the tramadol dosage when converting patients from another opioid can lead to a fatal overdose with the first dose.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
The concomitant use or discontinuation of cytochrome (CYP) P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol produces complex effects. Therefore, careful consideration on the effects of the concomitant use of these agents on tramadol (a weak serotonin and norepinephrine reuptake inhibitor and μ-opioid agonist) and M1 (which is more potent than tramadol in μ-opioid receptor binding) is required.

CYP2D6 and CYP3A4 inhibitors reduce the metabolic clearance and increase the plasma concentrations of tramadol, which can prolong its therapeutic effects and/or increase the risk for serious adverse events such as seizures and serotonin syndrome. CYP2D6 and CYP3A4 inhibitors also decrease the plasma M1 concentrations, which may result to reduced efficacy and in manifestations of opioid withdrawal signs and symptoms in patients who developed physical dependence to tramadol.

The concomitant use of tramadol with CYP450 2D6 or 3A4 inhibitors, or the discontinuation of a CYP450 3A4 inducer, may increase tramadol plasma concentrations, which could increase or prolong adverse reactions; increase the risk for serious adverse events (e.g., seizures and serotonin syndrome); and may cause potentially life-threatening respiratory depression.

The discontinuation of concomitantly used CYP450 2D6 or 3A4 inhibitors may decrease tramadol plasma levels and increase M1 plasma levels, which could consequently increase or prolong adverse reactions associated with opioid toxicity and may cause potentially life-threatening respiratory depression.

Monitor patients receiving tramadol and any CYP2D6 or 3A4 inhibitor for the risk of serious adverse events (e.g., seizures and serotonin syndrome), and signs and symptoms that may indicate opioid toxicity and opioid withdrawal.

Concomitant Use with Benzodiazepines or Other Central Nervous System (CNS) Depressants
The concurrent use of opioids with CNS depressants (e.g., benzodiazepines, non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol) can lead to profound sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of these drugs should be reserved for patients for whom alternative treatment options are inadequate. (See ***Interactions with Other Medicaments***)

The lowest effective dosages and minimum duration of concomitant use should be prescribed if benzodiazepines or other CNS depressant are to be concurrently used with opioid analgesics. In patients already administered with an opioid analgesic, a dose of the benzodiazepine or other CNS depressants lower than indicated in the absence of an opioid should be prescribed initially and subsequently titrate according to clinical response. If an opioid analgesic is to be prescribed in a patient already taking a benzodiazepine or other CNS depressant, a lower initial dose of the opioid analgesic should be prescribed, and titrate according to clinical response. Monitor patients closely for signs and symptoms of respiratory depression and sedation.

Patients and caregivers should be informed about the risks of respiratory depression and sedation when tramadol is concomitantly used with CNS depressants. Patients should be screened for risk of substance use disorders and should be informed of the risk of overdose and death associated with the use of additional CNS depressants. (See ***EFFECTS ON ABILITY TO DRIVE AND USE MACHINE***)

Serotonin Syndrome
Cases of serotonin syndrome, a potentially life-threatening condition, may occur with the use of tramadol within the recommended dose, particularly with concomitant use of serotonergic drugs; drugs that impair the metabolism of serotonin; and drugs that impair the metabolism of tramadol. (See ***Interactions with Other Medicaments***)

Serotonin syndrome symptoms may include the following: mental status changes (e.g., agitation, hallucinations, coma); autonomic instability (e.g., hyperthermia, labile blood pressure, tachycardia); neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity); and gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting). These symptoms may occur within several hours to a few days of concomitant administration of these drugs, but may occur at a later time. If serotonin syndrome is suspected, use of tramadol should be discontinued and supportive symptomatic treatment should be performed, depending on the nature and severity of symptoms.

Patients should be informed that opioids, when concomitantly administered with serotonergic drugs, could result to a rare but potentially life-threatening condition. Patients should be warned of the symptoms of serotonin syndrome, and to seek medical attention immediately if these symptoms occur. Instruct patient to notify their healthcare provider if they are currently taking, or planning to take serotonergic drugs.

Increased Risk of Seizures
Seizures have been reported in patients receiving tramadol even within the recommended dosage range. Seizure risk is increased in patients administered with tramadol doses above the recommended range. Seizures can also occur after the first dose. Concomitant use of tramadol increases seizure risk in patients taking:

- Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants or anorectics
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzapine, promethazine, etc.)
- Monoamine oxidase inhibitors (MAOIs)
- Antipsychotics or neuroleptics (e.g., haloperidol, droperidol, thioridazine)
- Other drugs that reduce seizure threshold
- Other opioids (See ***Interactions with Other Medicaments***)

Tramadol may also increase the risk of convulsions in patients with epilepsy; those with a history of seizures; or in patients with a recognized risk for seizure (e.g., head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). Administration of naloxone for tramadol overdose may increase the risk of seizure. Patients with epilepsy or those susceptible to seizures should be treated only if there are compelling situations.

Increased Risk of Suicide
Do not prescribe tramadol to patients who are suicidal or prone to addiction. (See ***Drug Abuse and Dependence***). Prescribe tramadol with caution in patients who:
Have a history of misuse and/or are currently taking CNS-active drugs (e.g., tranquilizers, antidepressant drugs, excessive alcohol) (See ***Interactions with Other Medicaments***)
Are suffering from emotional disturbance or depression

The cautious prescribing of tramadol is essential for the safe use of this drug. The use of non-narcotic analgesics for patients who are depressed or suicidal should be considered. Patients should be informed not to exceed the recommended dose and to limit their alcohol intake.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with the use of opioids, more often after greater than one month of use. Adrenal insufficiency may be manifested by non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, the diagnosis should be confirmed immediately with appropriate diagnostic testing. If adrenal insufficiency is diagnosed, the patient should be administered with physiologic replacement doses of corticosteroids. The patient may be weaned off from opioids to allow the recovery of adrenal function. Corticosteroid therapy should be continued until adrenal function recovers. Other opioids may be tried, since some cases reported that adrenal insufficiency did not recur with the use of different opioids.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic or Debilitated Patients
Tramadol should be administered cautiously in patients at risk for respiratory depression. The administration of tramadol at recommended dosages in patients with significant chronic obstructive pulmonary disease or cor pulmonale; and those with a substantially reduced respiratory reserve; hypoxia; hypercapnia; or pre-existing respiratory depression, poses a risk of decreased respiratory drive, including apnea. Patients who may have altered pharmacokinetics (elderly, cachectic, or debilitated patients) are also more likely to experience life-threatening respiratory depression. Consider alternative, non-opioid analgesics for these patients. Moreover, the concomitant administration of tramadol with other drugs that depress respiration must be avoided. Close monitoring for respiratory depression should be performed, especially during treatment initiation and following dosage increases. (See ***Interactions with Other Medicaments***)

Severe Hypotension
The use of tramadol in ambulatory patients may cause severe hypotension including orthostatic hypotension and syncope. The risk of severe hypotension is increased in patients with compromised ability to maintain blood pressure due to reduced blood volume or concomitant administration of certain CNS depressant drugs (See ***Interactions with Other Medicaments***).

Patients should be monitored for signs of hypotension after initiating or titrating the dosage of tramadol. The use of tramadol in patients with circulatory shock should be avoided, since tramadol may cause vasodilation that can further decrease the cardiac output in these patients.

Increased Intracranial Pressure or Head Trauma
Tramadol should be used with caution in patients with increased intracranial pressure, head trauma or tumor, shock, or a reduced level of consciousness of uncertain origin. The respiratory depressant effects of opiate agonists, which include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, may be markedly exaggerated in these patients. Also, pupillary changes (i.e., miosis) and other adverse events (e.g., confusion, vomiting) caused by tramadol may obscure the existence, extent or course of intracranial pathology. Tramadol should only be used with extreme caution and only if it is deemed necessary.

Patients should be monitored for signs of sedation and respiratory depression, especially during the initiation of tramadol therapy. Moreover, clinicians should maintain a high index of suspicion for adverse reactions when evaluating altered mental status in these patients administered with tramadol.

Anaphylaxis and Other Hypersensitivity Reactions
Serious fatal anaphylactic reactions have been rarely reported in patients receiving tramadol. These events often occur after the first dose. Other allergic reactions, such as pruritus, hives, bronchospasm, angioedema, TEN, and SJS, were also reported.

Patients with a higher risk for these anaphylactic reactions (e.g., patients with history of anaphylactoid reactions to codeine and other opioids) should not receive tramadol. If anaphylaxis or other hypersensitivity reactions occur, the administration of tramadol should be stopped immediately and discontinued permanently. Do not rechallenge with any tramadol-containing formulation. Patients should be instructed to seek immediate medical attention if any symptom of these hypersensitivity reactions occurred.

Hyponatremia
Hyponatremia has been rarely reported with the use of tramadol, usually in patients with predisposing risk factors [old age and/or using concomitant medications that may cause hyponatremia (e.g., antidepressants, benzodiazepines, diuretics)]. Some reports have demonstrated that hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hyponatremia can be resolved with discontinuation of tramadol and by appropriate treatment (e.g., fluid restriction). Patients with predisposing risk factors should be monitored for signs and symptoms of hyponatremia during tramadol therapy.

Gastrointestinal Conditions
Morphine-like opioids, including tramadol, have been demonstrated to decrease bowel motility. Tramadol may complicate the clinical assessment of patients with acute abdominal conditions. It may cause spasm of the sphincter of Oddi, while opioids may increase serum amylase levels. Patients with biliary tract disease, including acute pancreatitis, should be monitored for worsening of symptoms.

Concomitant Conditions in Adolescents
The use of tramadol in adolescents between 12 and 18 years old who are obese, or have conditions such as obstructive sleep apnea or severe lung disease is not recommended, due to the increased risk of serious breathing problems.

Breastfeeding
Breastfeeding is not recommended during tramadol therapy due to the risk of serious adverse reactions, including difficulty in breastfeeding, excessive sleepiness and serious breathing problems that may lead to death of the breastfed infant. (See ***Statement on Usage for High Risk Groups***)

Withdrawal
The use of mixed agonist/antagonist analgesics or partial agonists must be avoided in patients receiving a full opioid agonist analgesic, including tramadol. Do not abruptly discontinue tramadol in patient who developed physical dependence.

DRUG ABUSE AND DEPENDENCE

Abuse
Tramadol has μ-opioid agonist activity which may be abused and subject to criminal diversion.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena which is developed after repeated substance use and includes the following: impaired or difficult control over drug use; compulsive use; use for non-medical purposes; persistent use despite harm or risk of harm; craving; a higher priority given to drug usage compared to other activities and obligations, increased tolerance, and in some cases, physical withdrawal. Although relapse is common, drug addiction can be treated by utilizing a multidisciplinary approach.

Abuse and addiction are distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by coexisting tolerance and symptoms of physical dependence in all addicts. Furthermore, tramadol abuse may occur even in the absence of true addiction.

Proper assessment of the patient and periodic re-evaluation of therapy are appropriate measures that can help limit the potential abuse of tramadol.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous therapy with tramadol.

Dependence
Chronic therapy with opioids may lead to the development of tolerance and physical dependence.

Tolerance is the need for increasing doses to maintain the desired effect (e.g., analgesia) in the absence of disease progression or other external factors), and may occur to both the desired and undesired effects of drugs. Tolerance may develop at different rates for various effects.

Physical dependence may result to withdrawal symptoms if tramadol was abruptly discontinued or if the dosage was significantly reduced. Withdrawal may also be precipitated through the administration of opioid antagonists (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not be manifested to a clinically significant degree until after several days to weeks of continued opioid use.

Do not abruptly discontinue tramadol in patient who developed physical dependence, otherwise, symptoms of withdrawal reactions to tramadol (e.g., agitation, anxiety, nervousness, irritability, insomnia, hyperkinesia, tremor, pyrexia, myalgia, chills, gastrointestinal symptoms, restlessness, rhinorrhea, lacrimation, yawning, mydriasis, perspiration) may occur. Other symptoms, such as panic attacks, severe anxiety, hallucinations, paresthesias, tinnitus and unusual CNS symptoms (i.e., confusion, delusions, depersonalization, derealization, paranoia), are rarely seen. Withdrawal symptoms may be avoided by tapering the dose of the medicine at the time of discontinuation. The use of mixed agonist/antagonist analgesics or partial agonists must be avoided in patients receiving a full opioid agonist analgesic, including tramadol.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Results of tests and investigations did not show a risk of carcinogenicity, mutagenesis or impairment of fertility for tramadol in man.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Tramadol may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving and operating machinery. Caution patients to avoid these potentially hazardous tasks unless they can tolerate the effects of tramadol and know how they will react to the medication. Patients should also be warned about the combined effects of tramadol with other CNS depressants.

INTERACTIONS WITH OTHER MEDICAMENTS

CONCOMITANT DRUGS	EFFECTS
Carbamazepine	Carbamazepine increases the metabolism of tramadol; thus, may significantly decrease its analgesic effect and may shorten its duration of action. The risk of tramadol-associated seizures may also be increased. The concomitant use of these drugs is not recommended.
Cimetidine	Cimetidine, a CYP 450 inhibitor, has no clinically significant effect on tramadol's pharmacokinetics.
CNS Depressants (e.g., alcohol, general anesthetics, anxiolytics, phenothiazines, sedatives and hypnotics, other centrally acting analgesics, opiate agonists, tranquilizers, muscle relaxants, other illicit CNS depressant drugs)	The concomitant use of CNS depressants may result to additive respiratory depression, profound sedation, coma, and death. Use with caution and in reduced dosage. (See ***Warnings and Precautions***)
CYP2D6 Inhibitors [quinidine, antipsychotic agents (e.g., phenothiazines), antidepressants (e.g., fluoxetine, paroxetine, amitriptyline, bupropion)]	May reduce metabolic clearance of tramadol, thereby increasing the risk for serious adverse events, including seizures and serotonin syndrome (See ***Warnings and Precautions***)
CYP3A4 Inducers [rifampicin, St. John's Wort (*Hypericum perforatum*), phenytoin]	Due to the induction of hepatic metabolism, CYP3A4 inducers may decrease tramadol's plasma concentration, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who are physically dependent to tramadol.
CYP3A4 Inhibitors [macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors]	May reduce metabolic clearance of tramadol, thereby increasing the risk for serious adverse events, including seizures and serotonin syndrome (See ***Warnings and Precautions***)
Digoxin	Rare reports of digoxin toxicity have been revealed in post-marketing surveillance. Patients should be monitored for signs of digoxin toxicity and adjust dosage of digoxin as needed.
Drugs that lower seizure threshold (e.g., SSRIs, TCAs, antipsychotics, bupropion, mirtazapine, tetrahydrocannabinol)	Tramadol may induce convulsions and increase the potential for these drugs to cause convulsions. Careful observation of the patient is advised, particularly during treatment initiation and dose increases.
General anesthetic agents	In one study using nitrous oxide/tramadol anesthetic technique (with only intermittent administration of enflurane, as required), tramadol was reported to enhance intra-operative recall. Although tramadol can be used intraoperatively provided that anesthesia is maintained with a potent volatile or intravenous anesthetic, its use during potentially very light levels of general anesthesia should be avoided.
MAOIs (e.g., selegiline, phenelzine)	The use of MAOIs is contraindicated when used 14 days prior to tramadol treatment. MAOIs may increase the risk of adverse effects such as serotonin syndrome, seizures, or opioid toxicity.
Mixed Agonist-Antagonists and Partial Agonist Opioid Analgesics (e.g., butorphanol, buprenorphine, nalbuphine, pentazocine)	Mixed agonist-antagonists and partial agonist opioid analgesics may reduce the analgesic effect of tramadol and/or may precipitate withdrawal symptoms. Concomitant use of these drugs with tramadol should be avoided.
Ondansetron	In a limited number of studies, ondansetron increased the requirement of tramadol in patients with postoperative pain.
Oral Anticoagulant (e.g., warfarin)	Prolonged International Normalized Ratio (INR) and prothrombin time with major bleeding and extensive ecchymoses were reported with the concomitant use of tramadol and warfarin. Use with caution when giving these drugs concomitantly. INR should be closely monitored.
Serotonergic drugs [e.g., SSRIs, Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), MAOIs, TCAs, triptans, linezolid, lithium, mirtazapine, St. John's Wort]	The concomitant use of tramadol with serotonergic drugs increases the risk of serotonin syndrome. Use with caution, particularly during the initiation of tramadol treatment and during dose increases.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy

Pregnancy Category C. Tramadol crosses the placenta, and there are no adequate and well-controlled studies in pregnant women. Tramadol should not be used in pregnant women, unless the potential benefits outweigh the possible risks to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death, and still birth have been reported in postmarketing surveillance. Signs of neonatal opioid withdrawal syndrome should be observed in newborns and should be managed accordingly.

Labor and Delivery

The safe use of tramadol during pregnancy has not been established. Tramadol should not be used in pregnant women prior to or during labor when other analgesics are more appropriate unless the potential benefits outweigh the potential risks. The use of tramadol may affect the duration of labor due to its inhibitory actions on uterine contractions or facilitatory actions on cervical dilation.

Chronic use during pregnancy may lead to neonatal withdrawal symptoms (See ***Warnings and Precautions***). If tramadol will be used during labor, it may cause respiratory depression in the newborn. An opioid antagonist (e.g., naloxone) should be available to reverse the opioid-induced respiratory depression in the neonate. Monitor newborns exposed to tramadol during labor for signs of excess sedation and respiratory depression.

Tramadol has also been shown to cross the placenta. The effect of tramadol, if any, on the later growth, development and functional maturation of the child is unknown.

Lactation

The safety of tramadol in infants and newborns has not been studied. The use of tramadol as an obstetric preoperative medication or for post-delivery analgesia in breastfeeding mothers is not recommended. Low levels of tramadol have been detected in breastmilk. Instruct nursing mothers to monitor infants for unusually increased sleepiness, limpness, or breathing difficulties; and to seek medical care immediately. Withdrawal symptoms may occur in breastfed infants when tramadol maternal administration is stopped, or when breast-feeding is stopped.

Children (< 12 years old)

Tramadol is contraindicated in children younger than 12 years old. Its use in children is not recommended since the safety and efficacy of tramadol have not been established.

Elderly (> 65 years old)

Tramadol should be used with great caution in patients older than 65 years. A higher incidence of adverse events was observed in patients older than 65 years compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension, and dyspepsia.

Renal and Hepatic Impairment

Impaired renal function results in decreased rate and extent of excretion of tramadol and its active metabolite, M1, while their metabolism is reduced in patients with advanced hepatic cirrhosis. Adjust doses as necessary (see ***Dosage and Mode of Administration***). With the prolonged half-life in these conditions, achievement of steady-state is delayed, so it may take several days for elevated plasma concentrations to develop.

UNDESIRABLE EFFECTS

The most frequently reported adverse effects are dizziness and nausea. Other common effects include abdominal pain, anorexia, anxiety, confusion, constipation, coordination disturbance, dry mouth, euphoria, flatulence, headache, hypertonia, malaise, menopausal symptoms, miosis, nervousness, rash, sleep disorder, somnolence, insomnia, urinary frequency, urinary retention, vasodilation, visual disturbance, and vomiting.

Blood and lymphatic system disorders: Blood dyscrasias

Infections and infestations: Cellulitis, epididymitis, pneumonia

Immune system disorders: Allergic reactions, anaphylaxis, angioedema, bronchospasm, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, vesicles

Endocrine disorders: Androgen deficiency, syndrome of inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders: Adrenal insufficiency, changes in appetite, edema, hypoglycemia, hyponatremia

Psychiatric disorders: Changes in activity (usually suppression, occasionally increase), changes in cognitive capacity and sensorial capacity (e.g., decision behavior, perception disorders), depersonalization, depression, derealization, delusions, difficulty in attention, dysphoria, elation, emotional lability, hallucinations, hyperactivity, hypoactivity, mental status changes, mood changes, nightmares, panic attacks, suicidal tendencies

Nervous system disorders: Abnormal dreams, abnormal gait, agitation, amnesia, asthenia, cognitive disorder, convulsions, CNS stimulation, coma, delirium, difficulty in concentration, disorientation, dysgeusia, dyskinesia, dystonia, epileptiform convulsions, hyperkinesia, hyperreflexia, involuntary muscle contractions, irritability, migraine, motor weakness, movement disorder, paresthesia, seizure, sedation, serotonin syndrome, spasticity, speech disorders, trembling, tremor, vertigo

Eye disorders: Blurred vision, cataracts, mydriasis

Ear and Labyrinth disorders: Deafness, tinnitus

Cardiac Disorders: Arrhythmia, bradycardia, cardiac arrest, chest pain, myocardial infarction, myocardial ischemia, palpitations, pulmonary edema, tachycardia

Vascular disorders: Circulatory depression, flushing, hot flushes, hypertension, hypotension, orthostatic dysregulation (tendency to collapse and cardiovascular collapse), orthostatic or postural hypotension, peripheral ischemia, shock, syncope

Respiratory, thoracic and mediastinal disorders: Apnea, coughing, dyspnea, nasal symptoms, nasopharyngitis, pulmonary embolism, respiratory arrest, respiratory depression, sinusitis, sneezing, upper respiratory tract infection, wheezing, worsening of asthma, yawning

Gastrointestinal disorders: Appendicitis, bloating, diarrhea, dyspepsia, dysphagia, gastritis, gastroenteritis, gastrointestinal bleeding, gastrointestinal irritation (feeling of pressure in the stomach), pancreatitis, retching, sore throat, stomatitis, toothache

Hepatobiliary disorders: Cholecystitis, cholelithiasis, hepatitis, liver failure

Skin and subcutaneous tissue disorders: Dermatitis, piloerection, pruritus, sweating

Musculoskeletal and connective tissue disorders: Arthralgia, joint stiffness, joint swelling, muscle cramps, muscle injury, muscle spasms, muscle twitching, musculoskeletal pain, myalgia, osteoarthritis aggravated, rigors, shivering

Renal and urinary disorders: Dysuria, hematuria, micturition disorder, proteinuria, urinary tract infection

Reproductive system and breast disorders: Amenorrhea, decreased libido, erectile dysfunction, impotence, infertility, menstrual disorder

General disorders and administration site conditions: Asthenia, clamminess, chilliness, death, dependence, diaphoresis, fatigue, fever, hyperthermia, influenza-like symptoms, jittery feeling, lethargy, peripheral swelling, pyrexia, withdrawal syndrome

Investigations: Abnormal electrocardiogram (ECG), decreased hemoglobin, elevated liver enzymes, increased blood creatine phosphokinase, increased blood glucose concentrations, increased creatinine, weight decreased

Injury, poisoning and procedural complications: Accidental injury, contusions, falls, joint sprain

OVERDOSE AND TREATMENT

Potential serious consequences of tramadol overdosage include respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, pulmonary edema (in some cases), bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, seizures, cardiac arrest, and death. Death may occur within one hour of overdosage.

Deaths due to overdose with abuse and misuse of tramadol have been reported. Moreover, the risk of fatal overdose is further increased when tramadol is abused concomitantly with CNS depressants such as alcohol or opioids.

Primary attention should be given in re-establishing a patent and protected airway and maintaining adequate assisted or controlled ventilation, if needed. General supportive treatment (including oxygen and vasopressors) may also be employed in the management of circulatory shocks and pulmonary edema, as indicated. Naloxone may reverse some, but not all symptoms caused by tramadol overdosage. Serious arrhythmias or cardiac arrest will require advanced life-supporting measures.

Opioid antagonists (e.g., naloxone) should only be administered for the management of clinically significant respiratory or circulatory depression due to tramadol overdose. Although the administration of naloxone will only reverse some (but not all) symptoms caused by tramadol overdosage, it also increases the risk of seizure, for which intravenous diazepam may be given. In individuals who are physically dependent on opioids, the administration of an opioid antagonist should be started with care and by titration with smaller than usual doses of the antagonist to prevent the occurrence of acute withdrawal symptoms.

Since the duration of opioid reversal is expected to be less than the duration of action of tramadol, the patient should be carefully monitored until respiration normalizes.

Gastrointestinal decontamination with activated charcoal or by gastric lavage may also be performed within one to two hours of oral tramadol intoxication to remove any unabsorbed drug. Once the airway is protected, activated charcoal may be administered via nasogastric tube in patients who are not fully conscious or have impaired gag reflex. Gastrointestinal decontamination at a later time may only be useful in cases of overdosage with unusually large quantities.

Hemodialysis is not expected to be helpful for tramadol overdose because it only removes less than seven percent of the administered dose in a four-hour dialysis period.

STORAGE CONDITIONS
Tramadol HCl (Siverol 50mg Capsule)
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

Tramadol HCl (Siverol 50 mg/1mL and 100 mg/2mL Ampule Solution for Injection)
Store at temperatures not exceeding 30°C. Protect from light.
Keep the product out of sight and reach of children.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

AVAILABILITY
Tramadol HCl (Siverol) 50 mg capsule Foil strip of 4's, box of 100
Tramadol HCl (Siverol) 50 mg/1 mL Solution for Injection - Box of 1 ampule
Tramadol HCl (Siverol) 100 mg / 2 mL Solution for Injection - Box of 1 ampule

Date of First Authorization:
Tramadol HCl (Siverol) 50 mg Capsule - DR-XY20446 - 21 December 2007
Tramadol HCl (Siverol) 50 mg/1 mL Solution for Injection - DR-XY24854 - July 21,1999
Tramadol HCl (Siverol) 100 mg / 2 mL Solution for Injection - DR-XY24853 - July 21,1999

Solution for Injection
Manufactured by
AMHERST PARENTERALS, INC.
Sta. Rosa-Tagaytay Road, Don Jose, Sta. Rosa City, Laguna, Philippines
for UNILAB, Inc.
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Capsule
Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for UNILAB, Inc.
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Trusted Quality Healthcare

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