Size: width 120 mm x Length 420 mm

Tamadol™

(Tramadol HCl)

Highnoon

COMPOSITION
Tamadol 50mg capsule:
Each capsule contains: Tramadol HCl 50mg

DESCRIPTION
Tramadol hydrochloride are an opioid agonist. It is a centrally acting analgesic which possesses opioid agonist properties. The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethyl-amino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

MECHANISM OF ACTION
Tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Tramadol consists of two enantiomers, the (+)-isomer is predominantly active as an opioid with preferential activity for the μ-receptor. The (-)-isomer potentiates the analgesic effect of the (+)-isomer and is active as an inhibitor of noradrena-line and seroto-nin uptake thereby modifying the transmission of pain impulses. The analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the *O*-demethylated metabolite M1 to μ-opioid receptors. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

PHARMACOKINETICS
Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use. Plasma protein binding is about 20%. Tramadol is metabolized by N- and O- demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite O-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine as metabolites. Tramadol is widely distributed, crosses the placenta and appears in small amounts in breast milk. The elimination half-life is about 6 hours. Tramadol may be taken without regard to food.

INDICATIONS
- It is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve it for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:
- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

DOSAGE AND ADMINISTRATION
Initial Dosage
Tamadol Capsule: Start it at 25 mg/day and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg /day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, it can be administered (50 to 100 mg) as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.

Dosage in Patients with Hepatic Impairment
The recommended dose for adult patients with severe hepatic impairment is 50 mg every 12 hours.

Dosage in Patients with Renal Impairment
In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of it; be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by haemodialysis, dialysis patients can receive their regular dose on the day of dialysis.

Dosage in Geriatric Patients
Do not exceed a total dose of 300 mg/day in patients over 75 years old.

- Do not abruptly discontinue it in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.
- When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking this, there are a variety of factors that should be considered, including the dose the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose off the opioid gradually.
- It may be necessary to provide the patient with a lower dosage strength to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, agitation, anxiety, hyperkinesia, tremor, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances. Monitor patients closely for respiratory depression, especially within the first [24]-[72] hours of initiating therapy and following dosage increases with this and adjust the dosage accordingly.

CONTRAINDICATIONS
It is contraindicated for:
- All children younger than [12] years of age
- Postoperative management in children younger than [18] years of age following tonsillectomy and/or adenoidectomy
- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity to tramadol, any other component of this product or opioids
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last [14] days
- In patients suffering from acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products
- In patients with epilepsy not adequately controlled by treatment
- For use in narcotic withdrawal treatment

WARNING AND PRECAUTIONS
Addiction, Abuse and Misuse*:* Tramadol is an opioid, it exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Tramadol. Addiction can occur at recommended dosages and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Tramadol, and monitor all patients receiving Tramadol for the development of these behaviours and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

Life-Threatening Respiratory Depression*:* Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Tramadol, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of Tramadol. To reduce the risk of respiratory depression, proper dosing and titration of Tramadol are essential. Accidental ingestion of even one dose of Tramadol, especially by children, can result in respiratory depression and death due to an overdose of tramadol. Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children: Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Children with obstructive sleep apnoea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:
- It is contraindicated for all children younger than [12] years of age
- It is contraindicated for postoperative management in paediatric patients younger than [18] years of age following tonsillectomy and/or adenoidectomy
- Avoid the use of tramadol in adolescents [12] to [18] years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnoea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

Nursing Mothers: In nursing mothers, tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite *O*-desmethyltramadol (M1). A baby nursing from an ultra-rapid metabolizer mother taking tramadol could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with tramadol.

CYP2D6 Genetic Variability, Ultra-rapid Metabolizer: Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype This rapid conversion results in higher than expected serum M1 levels. Individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Individuals who are ultra-rapid metabolizers should not use tramadol.

Neonatal Opioid Withdrawal Syndrome: Prolonged use of tramadol during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated. Observe new-borns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes: The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol requires careful consideration of the effects on the parent drug, tramadol which is a weak serotonin and norepineph-rine reuptake inhibitor and μ-opioid agonist, and the active metabolite, M1, which is more potent than tramadol in μ-opioid receptor binding.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors: The concomitant use of tramadol with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. A decrease in M1 exposure in patients who have developed physical dependence to tramadol, may result in signs and symptoms of opioid withdrawal and reduced efficacy. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome. Discontinua-tion of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in tramadol plasma levels and an increase in active metabolite M1 levels, which could increase or prolong adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression. Follow patients receiving tramadol and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when tramadol is used in conjunction with inhibitors of CYP2D6.

Cytochrome P450 3A4 Interaction: The concomitant use of tramadol with cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in tramadol plasma concentrations, which could increase or prolong adverse reactions, increase the risk for serious adverse events including seizures and serotonin syndrome, and may cause potentially fatal respiratory depression. The concomitant use of tramadol with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower tramadol levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal. Follow patients receiving tramadol and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when tramadol is used in conjunction with inhibitors and inducers of CYP3A4.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants: Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Tramadol with benzodiazepines or other CNS depressants (e.g., non-benzo-diazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. 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 Tramadol is used with benzodiaze-pines 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.

Serotonin Syndrome Risk: C*ases* of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, particularly during concomitant use with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepineph-rine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, tremor, incoordination, rigidity), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea), spontaneous clonus, inducible or ocular clonus with agitation or diaphoresis, hypertonia and body temperature more than 38°C. The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later than that. Discontinue tramadol if serotonin syndrome is suspected.

Increased Risk of Seizure: Seizures have been reported in patients receiving tramadol within the recommended dosage range. Risk of seizure is increased with doses of tramadol above the recommended range. The concomitant use of tramadol increases the seizure risk in patients taking; Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics), Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), Other opioids [MAO inhibitors, Neuroleptics, or other drugs that reduce the seizure threshold]. Risk of seizure 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).

Suicide Risk: Do not prescribe tramadol for patients who are suicidal or addiction-prone. Consideration should be given to the use of non-narcotic analgesics in patients who are suicidal or depressed. It should be prescribed with caution for patients with a history of misuse and/or are currently taking CNS-active drugs including tranquilizers or antidepressant drugs, alcohol in excess, and patients who suffer from emotional disturbance or depression.

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, severe abdominal pain, extreme fatigue, decreased appetite, weight loss 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.
Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: The use of tramadol in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Tramadol; treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnoea, even at recommended dosages of tramadol.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating tramadol and when tramadol is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Severe Hypotension: Tramadol may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of tramadol. In patients with circulatory shock, it may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of tramadol in patients with circulatory shock.

Risks of use in Patients with Increased Intracranial Pressure, Brain Tumours, Head Injury, or Impaired Consciousness: In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumours), tramadol may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with tramadol. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of tramadol in patients with impaired conscious-ness or coma.

Risks of Use in Patients with Gastrointestinal Conditions: Tramadol is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. It may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Anaphylaxis and Other Hypersensitivity Reactions: Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol. When these events do occur, it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of hypersensitivity reactions to tramadol and other opioids may be at increased risk and therefore should not receive tramadol. If anaphylaxis or other hypersensitivity occurs, stop administration of tramadol immediately, discontinue it permanently, and do not rechallenge with any formulation of tramadol. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including tramadol. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

Driving and Operating Machinery: Tramadol may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of tramadol.

ADVERSE REACTIONS
The reported adverse events are: addiction, abuse, misuse, life threatening respiratory depression, ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children, neonatal opioid withdrawal syndrome, serotonin syndrome, seizures, suicide, adrenal insufficiency, severe hypotension, gastrointestinal adverse reactions , hypersensitivity reactions, dizziness, vertigo, nausea, constipation, headache, somnolence, vomiting, pruritus, CNS stimulation, asthenia, sweating, dyspepsia, dry mouth, diarrhoea, malaise, vasodilation, anxiety, confusion, coordination disturbance, euphoria, miosis, nervousness, sleep disorder, abdominal pain, anorexia, flatulence, hypertonia, rash, visual disturbance, menopausal symptoms, urinary frequency, urinary retention, accidental injury, allergic reaction, anaphylaxis, death, weight loss, mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, coma, worsening of asthma, orthostatic hypotension, syncope, tachycardia, bradycardia, abnormal gait, abnormal coordination, amnesia, cognitive dysfunction, depression, difficulty in concentration, hallucinations, paresthesia, tremor, dyspnoea, Stevens-Johnson Syndrome, toxic epidermal necrolysis, urticaria, vesicles, dysgeusia, dysuria, menstrual disorder, abnormal ECG, hypertension, hypotension, myocardial ischemia, palpitations, pulmonary oedema, pulmonary embolism., migraine, gastrointestinal bleeding, hepatitis, stomatitis, liver failure, creatinine increase, elevated liver enzymes, haemoglobin decrease, proteinuria, cataracts, deafness and tinnitus.
The additional reported adverse events are: androgen deficiency, QT prolongation and/or torsade de pointes, mydriasis, hypoglycaemia, movement disorder, speech disorder, hiccups, nightmares, dysphoria, blurred vision, wheezing, bronchospasm, motorial weakness and delirium.

DRUG INTERACTION
CYP2D6 Inhibitors:
The concomitant use of tramadol and CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine and bupropion) may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of tramadol is achieved. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase. This could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, such as potentially fatal respiratory depression. If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome.

CYP3A4 Inhibitors
The concomitant use of tramadol and CYP3A4 inhibitors such as [macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)] can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of tramadol is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to tramadol. If concomitant use is necessary, consider dosage reduction of tramadol until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the tramadol dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.

CYP3A4 Inducers
The concomitant use of tramadol and CYP3A4 inducers (rifampin, carbamazepine, phenytoin) can decrease the plasma concentra-tion of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause seizures, serotonin syndrome, and/or potentially fatal respiratory depression. If concomitant use is necessary, consider increasing the tramadol dosage until stable drug effects are achieved. If a CYP3A4 inducer is discontinued, consider tramadol dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol and carbamaze-pine is not recommended.

Serotonergic Drugs
The concomitant use of opioids with other drugs [i.e. Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepineph-rine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)] that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue tramadol immediately if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs)
MAOI (phenelzine, tranylcypromine, linezolid) interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). Do not use tramadol in patients taking MAOIs or within 14 days of stopping such treatment.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
Mixed agonist / antagonist and partial agonist opioid analgesic (butorphanol, nalbuphine, pentazocine, buprenorphine) may reduce the analgesic effect of tramadol and/or precipitate withdrawal symptoms. Avoid concomitant use.

Muscle Relaxants
Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of tramadol and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose.

Diuretics
Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic drugs
The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when tramadol is used concomitantly with anticholinergic drugs.

Digoxin
Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.

Warfarin
Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

Benzodiazepines and Other Central Nervous System (CNS) Depressants
The concomitant use of benzodiazepines or other CNS depressants (sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, and alcohol) increases the risk of respiratory depression, profound sedation, coma, and death. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.

USE IN SPECIFIC POPULATIONS
Pregnancy
Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome can present as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhoea 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 new-born. Observe new-borns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly. Neonatal seizures, neonatal withdrawal syndrome, foetal death and still birth have been reported.

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Tramadol is not recommended for use in pregnant women during or immediately prior to labour, when other analgesic techniques are more appropriate. Opioid analgesics, including tramadol, can prolong labour through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. Tramadol has been shown to cross the placenta.

Lactation
Tramadol is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and new-borns has not been studied. Tramadol and its metabolite, O-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with tramadol.

Female and male of reproductive potential contraception
Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Paediatric Use
The safety and effectiveness of tramadol in paediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol.
In some of the reported cases, these events followed tonsillecto-my and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnoea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:
- Tramadol is contraindicated for all children younger than [12] years of age
- Tramadol is contraindicated for postoperative management in paediatric patients younger than [18] years of age following tonsillectomy and/or adenoidectomy
- Avoid the use of tramadol in adolescents [12] to [18] years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnoea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

Geriatric Use
Respiratory depression is the chief risk for elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of tramadol slowly in geriatric patients starting at the low end of the dosing range and monitor closely for signs of central nervous system and respiratory depression. Tramadol is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment
Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction is recommended. With the prolonged half-life in this condition, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

Hepatic Impairment
Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver. In patients with severe hepatic impairment, dosing reduction is recommended. With the prolonged half-life in this condition, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

DRUG ABUSE AND DEPENDENCE
Abuse
Tramadol is a mu-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion. Tramadol, a substance with a high potential for abuse similar to other opioids. It can be abused and is subject to misuse, addiction, and criminal diversion. All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Tramadol capsule is intended for oral use only. The crushed capsules pose a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence
Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of drugs to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects. Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. Do not abruptly discontinue tramadol in a patient physically dependent on opioids. Rapid tapering of tramadol in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain and suicide. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs.

OVERDOSAGE
Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary oedema, bradycardia, QT prolongation, hypotension, partial or complete airway obstruction, atypical snoring, seizures, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations. In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary oedema as indicated. Cardiac arrest or serious arrhythmias will require advanced life-supporting measures. In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities. Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Haemodial-ysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

PRESENTATION
Tamadol 50mg Capsules:
Alu. PVC Blister Pack of 1 x 10's.

ٹیماڈول™

(ٹراماڈول ہائیڈروکلورائیڈ)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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Size: width 120 mm x Length 420 mm