120x380mm

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Seden-P™

(Tramadol HCl + Paracetamol)

Highnoon

COMPOSITION
Seden-P 37.5mg/325mg Tablet: Each film-coated tablet contains:
Tramadol HCl 37.5mg
Paracetamol 325mg

DESCRIPTION
Seden-P contains two analgesics, tramadol hydrochloride an opioid agonist, and paracetamol.

MECHANISM OF ACTION
Tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action of tramadol is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. 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. Paracetamol is a non-opioid, non-salicylate analgesic. The site and mechanism for the analgesic effect of paracetamol has not been determined but is thought to primarily involve central actions. It is known to inhibit the cyclooxygenase (COX) pathways. Paracetamol may inhibit the COX pathway in the central nervous system but not peripheral tissues. Paracetamol is thought to inhibit the synthesis of prostaglandins in the central nervous system.

PHARMACOKINETICS
Tramadol is readily absorbed after oral doses but is subject to first pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use and 100% after intramuscular injection. Plasma protein binding is about 20%. Tramadol is metabolized by N- and O-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation and sulfation in the liver. The metabolite O-desmthyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine as metabolites. Tramadol is widely distributed and crosses the placenta and appears in small amount in breast milk. The elimination half-life is about six hours.

Paracetamol is readily absorbed from gastrointestinal tract and peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed over most body tissues. It crosses the placenta and present in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugate. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (N -acetyle - p - benzoquininoneimine) is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

INDICATIONS AND USAGE
It is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

It is for short-term use of five days or less.
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve its use in patients for whom alternative treatment options (e.g., non-opioid analgesics) have not been tolerated, or are not expected to be tolerated or have not provided adequate analgesia, or are not expected to provide adequate analgesia.
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DOSAGE AND ADMINISTRATION
The initial dose of Seden-P is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. In patients with creatinine clearances of less than 30 mL/min, do not exceed 2 tablets every 12 hours.
Do not exceed the recommended dose. Do not co-administer with other tramadol or paracetamol containing products. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases and adjust the dosage accordingly. Do not abruptly discontinue in patients who may be physically dependent on opioids.

CONTRAINDICATIONS
- All children younger than 12 years of age.
- Post-operative 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.
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
- Previous hypersensitivity to tramadol, paracetamol, any other component of this product, or opioids. Hypersensitivity to the active substances or to any of the excipients.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days.
- Acute intoxication with alcohol, hypnotic drugs or centrally acting analgesics, opioids or psychotropic drugs.
- Severe hepatic impairment.
- Epilepsy not controlled by treatment.

ADVERSE REACTIONS
The reported adverse effects are palpitations, tachycardia, arrhythmia, postural hypotension, bradycardia, collapse, QT prolongation and/or torsade de pointes, vision blurred, miosis, mydriasis, tinnitus, nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence, dysphagia, melaena, changes in appetite, tongue edema, chills, chest pain, drug withdrawal syndrome, transaminases increased, hypoglycaemia, weight decreased, pyroglutamic acidosis (PGA), hepatotoxicity, dizziness, somnolence, headache, trembling, involuntary muscular contractions, motor weakness, paraesthesia, amnesia, ataxia, convulsions, syncope, speech disorders, serotonin syndrome, seizures, hypertonia, migraine, stupor, vertigo, confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders depression, hallucinations, nightmares, delirium, drug dependence, abuse, changes in mood (euphoric, dysphoria), changes in activity (suppression, increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders), suicide, anorexia, depersonalization, emotional lability, impotence, paroniria, abnormal thinking, albuminuria, micturition disorders (dysuria and urinary retention), adrenal insufficiency, oliguria, dyspnoea, hiccups, allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis, life-threatening respiratory depression, worsening of asthma, hyperhidrosis, pruritus, dermal reactions (e.g. rash, urticaria), increase sweating, hypertension, hypotension, hot flush, alterations of warfarin effect, including elevation in prothrombin times, blood dyscrasias, including thrombocytopenia, agranulocytosis, serotonin syndrome, symptoms of drug withdrawal syndrome, similar opiate withdrawal may occur including agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms, panic attacks, prostatic disorder, asthenia, fatigue, rigors, weight decrease, anaemia and abnormal hepatic function.

DRUG INTERACTIONS
- The concomitant use of this combination (tramadol and paracetamol) and CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine, 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 combination (tramadol and paracetamol) is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. 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 which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity and may cause 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. If a CYP2D6 inhibitor is discontinued, consider lowering this combination (tramadol and paracetamol) dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
- The concomitant use of this combination (tramadol and paracetamol) and CYP3A4 inhibitors [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 this combination (tramadol and paracetamol) 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 and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. If concomitant use is necessary, consider dosage reduction of this combination (tramadol and paracetamol) 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 this combination (tramadol and paracetamol) dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
- The concomitant use of this combination (tramadol and paracetamol) and CYP3A4 (rifampin, carbamazepine, phenytoin) inducers can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependene 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 serious respiratory depression, seizures and serotonin syndrome. If concomitant use is necessary, consider increasing the this combination (tramadol and paracetamol) dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider this combination (tramadol and paracetamol) 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 this combination (tramadol and paracetamol) and carbamazepine is not recommended.
- Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (benzodiazepines & other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol), can increase the risk of hypotension, 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. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.
- The concomitant use of opioids with other drugs 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 this combination (tramadol and paracetamol), if serotonin syndrome is suspected. Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine 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).
- Monoamine Oxidase Inhibitors (phenelzine, tranylcypromine, linezolid) interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). Do not use this combination (tramadol and paracetamol) in patients taking MAOIs or within 14 days of stopping such treatment.
- The mixed agonist / antagonist and partial agonist opioid analgesic (butorphanol, nalbuphine, pentazocine, buprenorphine) may reduce the analgesic effect of this combination (tramadol and paracetamol) and/or precipitate withdrawal symptoms. Avoid concomitant use.
- 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 this combination (tramadol and paracetamol) 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.
- 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.
- 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 this combination (tramadol and paracetamol) is used concomitantly with anticholinergic drugs.
- Rare reports of digoxin toxicity have been observed, follow the patients for sign of digoxin toxicity and adjust the dose of digoxin as needed.
- Rare reports of alteration of warfarin effect, including elevation of prothrombin time were observed. Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed. As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol/Paracetamol and warfarin like compounds are administered concurrently due to the reports of increased INR.

WARNINGS AND PRECAUTIONS
- Tramadol, an opioid, exposes users to the risks of addiction, abuse, and misuse. Addiction can occur at recommended dosages and if the drug is misused or abused. Prolonged use of this product may lead to drug dependence (addiction). The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression) or psychiatric conditions. Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. Overuse or misuse may result in overdose and/or death. Patients should be closely monitored for signs of misuse, abuse, or addiction.
- 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. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of this combination, the risk is greatest during the initiation of therapy or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration are essential. Overestimating the dosage of this combination when converting patients from another opioid product can result in a fatal overdose with the first dose. Accidental ingestion of even one dose of this product, 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 apnea (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.
- 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 younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Avoid usage 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 apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. As with adults, when prescribing opioids for adolescents, lowest effective dose should be chosen for the shortest period of time and patients and caregivers should be informed about its risks and opioid overdose.
- Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype. These individuals convert tramadol into its active metabolite, more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labelled dosage regimens, 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). Therefore, individuals who are ultra-rapid metabolizers should not use it.
- Prolonged use of this combination 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, and requires management according to protocols developed by neonatology experts.
- The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from this combination are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with this combination requires careful consideration of the effects on the parent drug, tramadol, which is a weak serotonin and norepinephrine reuptake inhibitor and μ-opioid agonist, and the active metabolite, M1, which is more potent than tramadol in μ-opioid receptor binding.
- The concomitant use 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. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome. Discontinuation 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.
- The concomitant use 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. Discontinuation 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.
- Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed 4,000 milligrams per day. The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking paracetamol.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine 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. 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. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.
- Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, including combination of tramadol & paracetamol, during concomitant use with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine 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, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinuation of this product is advised if serotonin syndrome is suspected.
- Seizures have been reported in patients receiving tramadol within the recommended dosage range. 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 (SSRIs) and Serotonin-norepinephrine re-uptake inhibitors (SNRIs) 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 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). In tramadol overdose, naloxone administration may increase the risk of seizure.
- Do not prescribe this product 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. Prescribe with caution for patients with a history of misuse and/or are currently taking CNS-active drugs including tranquilizers, or antidepressant drugs, or alcohol in excess, and patients who suffer from emotional disturbance or depression. Inform patients not to exceed the recommended dose and to limit their intake of alcohol.
- 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.
- Its use in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
  - o Tramadol/Paracetamol-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 apnea, even at recommended dosages of this combination.
  - o 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.

  Close monitoring is recommended for patients on drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.
- It 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 anaesthetics). Monitoring of such patients for signs of hypotension after initiating or titrating is advised. In patients with circulatory shock, it may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid its use in such conditions.
- In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), it may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury. Avoid its use in patients with impaired consciousness or coma.
- Rarely, paracetamol may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
- It is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The tramadol may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase.
- 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 anaphylactoid reactions to tramadol and other opioids may be at increased risk and therefore should not consume this combination. If anaphylaxis or other hypersensitivity occurs, stop administration of it immediately, discontinue this combination 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.
- There have been reports of hypersensitivity and anaphylaxis associated with the use of paracetamol. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Patients should discontinue this product immediately and seek medical care.
- Due to the potential for paracetamol hepatotoxicity at doses higher than the recommended dose, this combination should not be used concomitantly with other paracetamol containing products.
- Do not abruptly discontinue in a patient physically dependent on opioids. When discontinuing in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol and paracetamol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain. Additionally, 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 this combination. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.
- It 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 this combination and know how they will react to the medication.
- Hyponatremia (serum sodium < 135 mmol/L) has been reported with the use of tramadol, and many cases are severe (sodium level < 120 mmol/L). Most cases of hyponatremia occurred in females over the age of 65 and within the first week of therapy. In some reports, hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Monitor for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment with this combination, especially during initiation of therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue it.
- Cases of tramadol-associated hypoglycemia have been reported, some resulting in hospitalization. In most cases, patients had predisposing risk factors (e.g. diabetes). If hypoglycemia is suspected, monitor blood glucose levels and consider drug discontinuation as appropriate.

USE IN SPECIFIC POPULATIONS
Paediatric population:
The effective and safe use of this combination (Tramadol and Paracetamol) has not been established in children below the age of 12 years. Treatment is therefore not recommended in this popation. Life-threatening respiratory depression and death have occurred in children who received Tramadol.

Elderly patients:
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. Therefore, if necessary, the dosage interval the dosage interval is to be extended according to the patient's requirements. In patients over 75 years old, it is recommended that the minimum interval between doses should not be less than 6 hours, due to the presence of tramadol.

Renal insufficiency/dialysis:
In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirement. Due to the presence of tramadol, the use of this combination (Tramadol and Paracetamol) is not recommended in patients with severe renal failure (creatinine clearance < 10 ml/min). In cases of moderate renal failure (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by hemofiltration, post-dialysis administration to maintain analgesia is not usually required.

Hepatic insufficiency
In patients with hepatic impairment the elimination of tramadol is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. This combination (tramadol hydrochloride and paracetamol) should not be used in patients with severe hepatic impairment.

Pregnancy:
This product is a fixed dose combination containing tramadol and paracetamol. This fixed having an active ingredient including tramadol, it should not be used during pregnancy. Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation. Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency. It is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. 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. It is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Tramadol has been shown to cross the placenta.

Nursing Mothers:
It should not be ingested during breast feeding. Administration to nursing women is not recommended as tramadol may be secreted in breast milk and may cause respiratory depression in the infant. 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 O-desmethyltramadol (M1). A baby nursing from an ultra-rapid metabolizer mother taking this combination could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression.
Paracetamol is excreted in breast milk, but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient
medicinal products containing only paracetamol.
Females and Males of Reproductive Potential
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.

OVERDOSAGE
The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following an paracetamol overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Symptoms of an overdose from tramadol: In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include, in particular: miosis, vomiting, cardiovascular collapse, consciousness disorders including coma, convulsions and respiratory depression, including respiratory arrest. Serotonin syndrome has also been reported. Symptoms of overdose from paracetamol: An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are: pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmia and pancreatitis have been reported. Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excessive quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue.

Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions.
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose, in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of the overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures, such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. Naloxone should be used to reverse respiratory depression; fits may be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or hemofiltration. Therefore, treatment with of acute intoxication with Tramadol/Paracetamol with haemodialysis or hemofiltration alone is not suitable for detoxification.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours, or any child taking ≥150 mg/kg of paracetamol in the preceding 4 hours, should undergo gastric lavage.

Paracetamol concentrations in blood should be measured more than 4 hours after an overdose, in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetyl cysteine (NAC), which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when a massive overdose is suspected. General supportive measures must be available. Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose

DOSAGE & 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 30ºC. Keep in a dry place. Protect from light.

PRESENTATION
Seden-P 37.5mg/325mg Tablets: Alu. PVC. Blister Pack of 2 x 5's.

سیڈن۔پی™

(ٹرامادول ہائیڈروکلورائیڈ + پیراسیٹامول)

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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۔
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