Dolpar 37.5mg/325mg

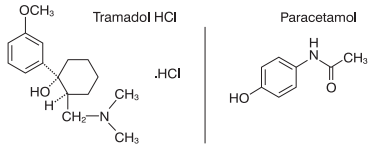
(Tramadol HCl / Paracetamol)
Tablets U.S.P.

COMPOSITION:
Each film-coated tablet contains:
Tramadol HCl U.S.P 37.5mg
Paracetamol U.S.P. 325mg

WARNING: addiction, abuse, and misuse; lifethreatening respiratory depression; accidental ingestion; ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children; neonatal opioid withdrawal syndrome; interactions with drugs affecting cytochrome p450 isoenzymes; hepatotoxicity; and risks from concomitant use with benzodiazepines or other cns depressants

DESCRIPTION: Tramadol Hydrochloride is freely soluble in water, while Paracetamol is sparingly soluble. Both drug substances are the subject of pharmacopoeia monographs. Tramadol and paracetamol are well absorbed from the film-coated tablet. Both drug substances in the combination tablet are bioequivalent to coresponding single agent solid oral dose forms and to oral solutions of the active ingredients.

Chemical Structure:



PHARMACOLOGICAL ACTION: Tramadol is a centrally acting synthetic analgesic compound whose analgesic profile can be attributed to the binding of parent and 0-demethylated (M1) metabolite to μ-opioid receptors as well as the weak inhibition of neuronal re-uptake of noradrenaline and serotonin. Paracetamol also has centrally acting analgesic effects. Tramadol is well absorbed after oral administration, reaching peak activity in 2 to 3 hours. The mean absolute bioavailability of a single 100 mg oral dose is approximately 75%, increasing to approximately 90% with multiple dosing. Oral absorption of paracetamol following administration of Tramadol HCl Paracetamol gives a peak plasma concentration of paracetamol within one hour and is not affected by co-administration with tramadol. Tramadol and paracetamol are both extensively metabolised in the liver. Approximately 30% of tramadol is excreted unchanged in the urine. Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. The half-life of paracetamol is about 2-3 hours in adults. Less than 9% of paracetamol is excreted unchanged in the urine.

INDICATIONS: Dolpar is indicated for the short-term treatment (i.e. three days or less) of mild to moderate acute pain.

CONTRAINDICATIONS: Tramadol HCl and Paracetamol is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol or other opioids such as codeine. It is also contraindicated in cases of severe liver function impairment and in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines. It should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal. Tramadol HCl and Paracetamol must not be used for narcotic withdrawal treatment. Tramadol HCl and Paracetamol should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions. Tramadol HCl and Paracetamol should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease. Safety during pregnancy and lactation has not been established. Tramadol has been shown to cross the placenta.

WARNINGS: Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should take paracetamol containing products under medical supervision. Tramadol may only be taken with special care in opioid dependence, reduced level of consciousness of uncertain origin, disorders of the respiratory function and increased intracranial pressure. **Seizures:** Seizures have been reported in patients receiving tramadol at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics. The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with a recognised risk for seizures e.g. drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramadol. **Drug Abuse and Dependence:** Although tramadol has a low dependence potential, tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop with long-term use. The drug has been associated with craving drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol have been reported. Tramadol should not be used in opioid-dependent patients. Tramadol can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with tramadol is not recommended. **Effects on ability to drive or operate machinery:** Tramadol may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired. This applies particularly in conjunction with other psychotropic medicines including alcohol.

DOSAGE AND DIRECTIONS FOR USE: To be used in adults and children over 16 years of age. Do not exceed the recommended dose. **Acute pain:** 2 tablets every 4 to 6 hours as needed for pain relief. Do not exceed 8 tablets per day.
Renal impairment: For patients with creatinine clearance <30 mL/min, the dosing interval of Dolpar should be increased not to exceed 2 tablets every to 12 hours.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS: The most frequently reported side effects were of the gastrointestinal and central nervous systems. These include: **Gastrointestinal system:** Nausea; abdominal pain, constipation, flatulence, vomiting; dry mouth; dyspepsia and diarrhoea. **Central Nervous System and Psychiatric:** Dizziness, headache, nervousness, anxiety, agitation, euphoria, emotional lability, hallucinations, hypertonia and tremor. Somnolence, insomnia, anorexia, anxiety, confusion, euphoria and nervousness. Other reported side-effects include pruritus, fatigue, upper respiratory tract infection, increased sweating, hot flushes, rashes and asthenia. Other side-effects reported with the use of tramadol include: anaphylaxis, increased liver enzyme values, postural hypotension or cardiovascular collapse and the potential for Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome. Paracetamol may cause allergic reactions and skin rash. The rash usually appears as red areas or allergic wheals, and may be accompanied by fever and involvement of the mucous membranes. The use of paracetamol has been associated with the occurrence of neutropenia, pancytopenia and leucopenia.

SPECIAL PRECAUTIONS: Do not co-administer Dolpar with other tramadol or paracetamol containing products. Tramadol HCl and Paracetamol should not be taken with alcohol containing beverages. The administration of Dolpar concurrently with central nervous system (CNS) depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquilizers or sedative hypnotics is likely to intensify and prolong CNS effects. Dolpar should be used with caution in patients with impaired renal function and in patients prone to convulsive disorders or in shock.

DRUG INTERACTIONS: Concomitant administration of Dolpar and carbamazepine may cause significantly decreased tramadol and M1 concentrations. Patients receiving carbamazepine may have significantly reduced analgesic effect from the tramadol component of Tramadol HCl and Paracetamol. Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline could result in some inhibition of the metabolism of tramadol. Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore, no alteration of the Tramadol HCl and Paracetamol dosage regimen is recommended for patients receiving chronic cimetidine therapy. Tramadol HCl Paracetamol must not be combined with a MAO-inhibitor, or within 14 days of discontinuation of it, as potentiation of serotonergic and noradrenergic effects may result. Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and rare alterations of warfarin effect including elevation of prothrombin times. Periodic evaluation of prothrombin time should be performed when Tramadol HCl and Paracetamol is administered concurrently with warfarin like compounds. Concomitant administration of diflunisal and paracetamol produces a 50% increase in paracetamol plasma levels in normal volunteers. Tramadol HCl and Paracetamol should be used cautiously and patients should be monitored carefully.

Known Symptoms of Overdose and Particulars of its treatment: The clinical presentation of overdosage 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. Primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all symptoms caused by overdosage, the risk of seizures is also increased with naloxone administration. Treatment of restlessness and/or convulsions is symptomatic and supportive (benzodiazepines/barbiturates). Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with Dolpar with haemodialysis or haemofiltration alone is therefore not suitable for detoxification. 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. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias have been reported. Symptoms during the first 2 days of acute poisoning do not reflect the potential seriousness of the overdosage. Nausea, vomiting, anorexia and abdominal pain may persist for a week or more. Liver injury may become manifest on the second day, (or later) initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time. The liver damage may progress to encephalopathy, coma and death. Cerebral oedema and non-specific myocardial depression have also occurred. In the event of overdosage consult a doctor or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible. Prompt treatment is essential. Any patient who has ingested about 7,5 g of paracetamol in the preceding 4 hours should undergo gastric lavage. Specific therapy with an antidote such as acetylcysteine or methionine may be necessary. If decided upon, acetylcysteine should be administered intravenously as soon as possible.
Acetylcysteine: Acetylcysteine should be administered as soon as possible, preferably within 8 hours of overdosage.
Intravenously: An initial dose of 150 mg/kg in 200 mL glucose injection, given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 mL of glucose injection over the next 4 hours, and then 100 mg/kg in 1000 mL over the next 16 hours. The volume of intravenous fluids should be modified for children. **Orally:** 140 mg/kg as a 5% solution initially, followed by a 70 mg/kg solution every 4 hours for 17 doses. Acetylcysteine is effective if administered within 8 hours of overdosage.

INSTRUCTIONS: Dosage as directed by the physician.
Store below 30°C.
Protect from heat, light and moisture.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

PRESENTATION: Dolpar (Tramadol HCl / Paracetamol) tablets U.S.P. are available in Alu/Alu blister pack of 1x10's with leaf insert.

Manufactured for:
DANEEN PHARMA **Daneen Pharma (Pvt.) Ltd.**
27-Sundar Industrial Estate, Sundar Raiwind Road Lahore, Pakistan.
Tel: +92-42-35297781-2, **Email:** info@daneenpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.daneenpharma.com

Manufactured by:
GENIX **Genix Pharma (Pvt.) Ltd.**
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.genixpharma.com