Paranext-T

(USP Specifications)

Tramadol HCl + Paracetamol (37.5mg/325mg)

Composition:
Paranext-T 37.5mg/325mg Tablet
Each film-coated tablet contains:
Tramadol HCl ..... 37.5mg (USP Specifications)
Paracetamol ..... 325mg (BP Specifications)

Clinical Particulars
Therapeutic indications:
Paranext-T is used to treat moderate to severe pain when your doctor recommends that a combination of tramadol hydrochloride and paracetamol is needed.
Clinical Pharmacology
Pharmacodynamics:
Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics ; tramadol and paracetamol.
ATC code: N02A J 13
ANALGESICS
Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonists of theμ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an anti tussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine. The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.
Pharmacokinetics:
Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol. After a single oral administration of a Paranext-T (37.5 mg/325 mg) tablet, peak plasma concentrations of64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 μg/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives t1/2 are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2,5 h (paracetamol).During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol hydrochloride/Paracetamol, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.
Absorption:
Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %. After administration of Tramadol hydrochloride/Paracetamol, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol. The oral administration of Tramadol hydrochloride/Paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that Tramadol hydrochloride/Paracetamol can be taken independently of meal times.
Distribution:
Tramadol has a high tissue affinity (Vd,β=203 ± 40 l). It has a plasma protein binding of about 20%. Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (˜20%) of paracetamol is bound to plasma proteins.
Metabolism:
Tramadol is extensively metabolized after oral administration. About 30 % of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. Tramadol is metabolised through O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.
Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.
Elimination:
Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.
Drug interactions:
Concomitant use is contraindicated with:
• Non-selective MAO Inhibitors Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.
• Selective-A MAO Inhibitors Extrapolation from non-selective MAO inhibitors Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.
• Selective-B MAO Inhibitors Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma. In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol.
Concomitant use is not recommended with:
• Alcohol
Alcohol increases the sedative effect of opioid analgesics. The effect on alertness can make driving of vehicles and the use of machines dangerous. Avoid intake of alcoholic drinks and of medicinal products containing alcohol.
• Carbamazepine and other enzyme inducers. Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.
• Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine) Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.
Concomitant use which needs to be taken into consideration:
• Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.
• Concomitant therapeutic use of tramadol and serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic anti-depressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition.
• Other opioid derivatives (including antitussive drugs and substitutive treatments) Increased risk of respiratory depression which can be fatal in cases of overdose.
• Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen. These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
• Sedating medicinal products such as benzodiazepines or related substances: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of the concomitant use should be limited.
• As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol hydrochloride/Paracetamol and warfarin like compounds are administered concurrently due to reports of increased INR.
• In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.
• Caution should be taken when paracetamol is used concomitantly with flucloxacillin, as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors.
Fertility, pregnancy and lactation
Pregnancy
Since this medicine is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.
Breast-feeding:
Since this medicine is a fixed combination of active ingredients including tramadol, it should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with Paranext-T. Discontinuation of breast-feeding is generally not necessary following a single dose of Paranext-T.
Fertility
Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.
Dosage and administration:
Swallow the tablets whole with sufficient liquid. Do not break or chew the tablets. Take Paranext-T for as short a time as possible and no longer than your doctor has told you.
Adults and adolescents over 12 years
The recommended dosage is to start with 2 tablets, unless otherwise prescribed by your doctor. If required, further doses may be taken, as instructed by your doctor. The shortest time between doses must be at least 6 hours. Do not take more than 8 tablets per day. Your doctor may increase the time between doses if: you are older than 75 years you have kidney problems you have liver problems.
Children under 12 years of age
Not recommended If you think that the effect of Paranext-T is too strong (you feel very drowsy or have difficulty breathing) or too weak (you do not have enough pain relief), contact your doctor. The maximum daily dose is 8 tablets per day (equivalent to 300 mg of tramadol and 2600 mg of paracetamol). Do not exceed this dose from this or other medicines
Contraindications:
• Hypersensitivity to the active substance or to any of the excipients
• acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs
• Tramadol hydrochloride/Paracetamol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal severe hepatic impairment, -epilepsy not controlled by treatment
Adverse reactions:
Tramadol
• Postural hypotension, bradycardia, collapse (tramadol).
• Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
• Rare cases: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
• Rare cases: changes in appetite, motor weakness, and respiratory depression
• Psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature(depending on personality and duration of medication). These include changes in mood, (usually euphoric mood occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders).
• Worsening of asthma has been reported though a causal relationship has not been established.
• Nervous system disorders: Not known: Serotonin syndrome.
• Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.
• Respiratory, thoracic and mediastinal disorders: frequency not known: hiccups.
Paracetamol
• Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
• There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.
• Very rare cases of serious skin reactions have been reported.
• Metabolism and nutrition disorders: cases of pyroglutamic acidosis (PGA) were reported with frequency not known, when paracetamol is used alone or with concomitant treatment of flucloxacillin, especially in patients with risk factors and prolonged treatment
Overdosage symptoms:
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 arrhythmias 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 excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Emergency treatment:
- 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 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 can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol hydrochloride/Paracetamol with haemodialysis or haemofiltration 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 who has ingested ≥150mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after 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-acetylcysteine (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 begiven 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 massive overdose is suspected. General supportive measures must beavailable.

Warnings and precautions:
Talk to your doctor or pharmacist before taking Paranext-T if you:
- Take other medicines containing paracetamol or tramadol
- Have liver problems or disease as your eyes and skin may turn yellow, which may suggest jaundice.
- Have kidney problems
- Have severe difficulties in breathing, for example asthma or severe lung problems.
- Have epilepsy or have already experienced fits or seizures
- Have recently suffered from a head injury, shock or severe headaches associated with vomiting (being sick).
- Are dependent on any medicine (for example morphine)
- Take other medicines to treat pain that contain buprenorphine, nalbuphine or pentazocine
- Are going to have an anesthetic (tell your doctor or dentist that you are taking Paranext-T 2

Dosage & Instructions:
Use as directed by the physician. For details, see enclosed leaflet.To be sold on the prescription of a registered medical practitioner only. Keep all medicines out of the reach of children.

Storage:
Store at 20°C-25°C. Protect from light and moisture. (excursions permitted to 15°C-30°C)

How supplied:
Paranext-T 37.5mg/325mg Tablets: Pack of 10 film-coated tablets.

Lactose and Gluten Free

پیرانیکسٹ-ٹی

(ٹرامادول ہائیڈروکلورائیڈ+پیراسیٹامول)

37.5 ملی گرام + 325 ملی گرام فلم کوٹڈ گولیاں

خوراک وہدایات:

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 20°C-25°C درجہ حرارت پر خشک اور روشنی سے محفوظ رکھیں۔

(درجہ حرارت کی حد 15°C سے 30°C ہے۔)

NEXT PHARMACEUTICAL
Manufactured by:
NEXT Pharmaceutical Products (Pvt.) Ltd.
Plot no. 44-A&B, Sunder Industrial Estate Lahore-Pakistan