Tramax-P Tablet

(Tramadol HCl + Paracetamol)

ٹریمیکس - پی ٹیبلیٹ

(ٹرماڈول ایچ سی ایل + پیراسیٹاموں)

COMPOSITION

TRAMAX-P Tablet

Each film-coated tablet contains:

Tramadol HCl.....37.5mg

Paracetamol.....325mg

(USP Specification)

DESCRIPTION

TRAMAX-P is used to relieve moderate pain. It is similar to narcotic pain medications. It works on certain nerves in the brain that control how you experience pain.

MODE OF ACTION

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Tramadol Hydrochloride/Paracetamol is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

INDICATIONS

TRAMAX-P tabletis indicated for the symptomatic treatment of moderate to severe pain.

The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.

DOSAGE & ADMINISTRATION

Adults and adolescents (12 years and older)

The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.

The dose should be individually adjusted according to intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

An initial dose of two tablets of Tramadol hydrochloride/Paracetamol is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Tramadol hydrochloride/Paracetamol should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with Tramadol hydrochloride/Paracetamol is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Pediatric population

The effective and safe use of Tramadol hydrochloride/Paracetamol has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

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 is to be extended according to the patient's requirements.

Renal insufficiency/dialysis

Because of the presence of tramadol, the use of Tramadol hydrochloride/Paracetamol is not recommended in patients with severe renal insufficiency (creatinine clearance < 10 ml/min). In cases of moderate renal insufficiency (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 haemofiltration, post dialysis administration to maintain analgesia is not usually required.

Hepatic impairment

In patients with hepatic impairment the elimination of tramadol is delayed. In these patients prolongation of dosage intervals should be carefully considered according to the patient's requirements.Because of the presence of paracetamol Tramadol hydrochloride/Paracetamol should not be used in patients with severe hepatic impairment

Method of administration

Oral use

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

PHARMACOKINETICS

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.

Biotransformation

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 are 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 P450 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 3 hours 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.

SIDE EFFECTS

The most commonly reported undesirable effects during the clinical trials performed with the Tramadol Hydrochloride/Paracetamol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

- ***Cardiovascular system disorders:***
- Uncommon (≥ 1/1000 to < 1/100): hypertension, palpitations, tachycardia, and arrhythmia
- ***Central and peripheral nervous system disorders:***
- Very common (≥ 1/10): dizziness, somnolence
- Common (≥ 1/100 to < 1/10): headache trembling
- Uncommon (≥ 1/1000 to < 1/100): involuntary muscular contractions, paraesthesia, and tinnitus
- Rare (≥ 1/10000 to < 1/1000): ataxia, convulsions, syncope

- ***Psychiatric disorders:***
- Common (≥ 1/100 to < 1/10): confusion, mood changes (anxiety, nervousness, and euphoria), sleep disorders
- Uncommon (≥ 1/1000 to < 1/100): depression, hallucinations, nightmares, amnesia
- Rare (≥ 1/10000 to < 1/1000): drug dependence.
- ***Post marketing surveillance:***
- Very rare (< 1/10000): abuse.
- ***Vision disorders:***
- Rare (≥ 1/10000 to < 1/1000): blurred vision
- ***Respiratory system disorders:***
- Uncommon (≥ 1/1000 to < 1/100): dyspnea
- ***Gastro-intestinal disorders:***
- Very common (≥ 1/10): nausea
- Common (≥ 1/100 to < 1/10): vomiting, constipation, dry mouth, diarrhea abdominal pain, dyspepsia, flatulence
- Uncommon (≥ 1/1000 to < 1/100): dysphagia, melena
- ***Liver and biliary system disorders:***
- Uncommon (≥ 1/1000 to < 1/100): hepatic transaminases increase
- ***Skin and appendages disorders:***
- Common (≥ 1/100 to < 1/10): sweating, pruritus
- Uncommon (≥ 1/1000 to < 1/100): dermal reactions (e.g. rash, urticaria)
- ***Urinary system disorders:***
- Uncommon (≥ 1/1000 to < 1/100): albuminuria, micturition disorders (dysuria and urinary retention)
- ***Body as a whole:***
- Uncommon (≥ 1/1000 to < 1/100): shivers, hot flushes, thoracic pain.
- ***Metabolism and nutrition disorders:***
- Unknown: hypoglycemia

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol cannot be excluded:

PRECAUTIONS

Tramadol hydrochloride/Paracetamol should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.

Paracetamol over dosage may cause hepatic toxicity in some patients.

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur even at therapeutic doses and for short-term treatment Withdrawal symptoms may be avoided by taper it at the time of discontinuation especially after long treatment periods. Rarely, cases of dependence and abuse have been reported

DRUG INTERACTIONS

- Non-selective MAO Inhibitors

Risk of serotoninergic syndrome: diarrhea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

- Selective-A MAO Inhibitors

Extrapolation from non-selective MAO inhibitors, risk of serotoninergic syndrome: diarrhea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

- Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotoninergic 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 other 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 (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity.

Serotonin syndrome is likely if when one of the following is observed:

Spontaneous clonus
- Inducible or ocular clonus with, agitation or diaphoresis
- Tremor and hyperreflexia,
- Hypertonia and body temperature >38°C and inducible or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

- Other opioid derivatives (including antitussive medicinal products and substitutive treatments), benzodiazepines and barbiturates: 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), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicinal products, thalidomide and baclofen. These active substances can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

- Caution should be exercised during concomitant treatment with Tramadol hydrochloride/Paracetamol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

- Other drugs known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.

- 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.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients
- Acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products
- 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.

STORAGE & INSTRUCTIONS

Store between 15-25°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on prescription of registered medical practitioner only.

HOW SUPPLIED

Tramax-p Tablet
10 's Tablets.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549, Sundar Industrial Estate,
Lahore-Pakistan.