TRAPADOL TAB.

COMPOSITION :

Each uncoated bilayered tablet contains:
Tramadol Hcl I.P. 37.5mg.
Paracetamol I.P. 325mg.

DESCRIPTION :

Tramadol 37.5 mg. and Paracetamol 325 mg. is an orally administered fixed-dose combination of the atypical opioid Tramadol and Paracetamol, which is indicated for the symptomatic treatment of moderate to severe pain. Fixed-dose Tramadol and Paracetamol is a rapidly-acting, longer duration of action, multimodal analgesic, which is effective and generally well tolerated in patients with moderate to severe pain. In several clinical studies has established that single or multiple dose Tramadol and Paracetamol was effective in providing pain relief in adult patients with postoperative pain after minor surgery, musculoskeletal pain like acute or chronic, painful diabetic peripheral neuropathy or migraine pain. It was also effective as an add-on analgesic in patients who were experiencing moderate to severe musculoskeletal pain like osteoarthritis or rheumatoid arthritis pain despite ongoing NSAID and/or disease-modifying antirheumatic drug therapy.

CLINICAL PHARMACOLOGY :

Pharmacodynamics

Tramadol –

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests it stablished that Tramadol has two mechanisms of action. First, it works by binding of parent Tramadol and its metabolite O-demethylated Tramadol (M1) to μ-opioid receptors and second weak inhibition of reuptake 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. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

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.

Apart from analgesia, tramadol administration may produce a constellation of symptoms like dizziness, somnolence, nausea, constipation, sweating and pruritus similar to that of other opioids.

Paracetamol –

Paracetamol is acetanilide derivative, non narcotic analgesic and antipyretic action with weak anti-inflammatory activity. It produces analgesia by increasing pain threshold and antipyresis by acting on the hypothalamic heat-regulating centre.
Paracetamol has analgesic and antipyretic action. It is more active on cyclo-oxygenase enzyme in brain. Peripherally it is a poor inhibitor of prostaglandin synthesis.

Paracetamol lowers fever by direct action on the thermoregulatory centre in the hypothalamus and block the effects of endogenous pyrogen.

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

Pharmacodynamic-

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 Tramadol-37.5mg and Paracetamol-325mg. tablet, peak plasma concentrations of 64.3 ng/ml of (+)-tramadol and 55.5 ng/ml (-)-tramadol are reached after 1.8 hours and 4.2 µg/ml of Paracetamol reached after 0.9 h respectively.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The absolute bioavailability of Tramadol HCl 37.5mg and Paracetamol 325mg. tablet has not been determined. The mean absolute bioavailability of a single 100mg dose is approximately 75%. After repeated administration, the bioavailability is increased and reaches approximately 90%.

After administration of Tramadol hydrochloride and Paracetamol tablet the oral absorption of paracetamol is rapid and nearly complete and absorption takes place mainly in the small intestine.

The oral administration of Tramadol hydrochloride and 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 and Paracetamol can be taken independently of meal times.

Distribution

Tramadol has a high tissue affinity. 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 approximately 20% of Paracetamol is bound to plasma proteins.

Metabolism

Following oral administration, Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (O-Desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response.

Paracetamol (Acetaminophen) is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways like-
(a) Conjugation with glucuronide, **(b)** Conjugation with sulfate and **(c)** Oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic Tramadol and M1 are approximately 5–6 and 7 hours, respectively, after administration of Tramadol HCl-37.5mg and Paracetamol- 325mg. The apparent plasma elimination half-life of racemic tramadol increased to 7–9 hours upon multiple dosing of Tramadol HCl 37.5mg and Paracetamol 325mg tablets.

The half-life of Paracetamol is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of Paracetamol is excreted unchanged in the urine.

THERAPEUTIC INDICATIONS :

Tramadol hydrochloride and Paracetamol tablets are indicated for the symptomatic treatment of moderate to severe pain. The use of this drug should be restricted to patients whose moderate to severe pain is considered to be required this combination.

DOSES :

Adults and adolescents (12 years and older)

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 is recommended. Additional doses can be taken as needed, not exceeding 8 tablets i.e. equivalent to 300mg Tramadol and 2600mg Paracetamol per day. The dosing interval should not be less than six hours.

This fixed dose combination of drug should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with this drug is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place to assess whether continuation of the treatment is necessary.

Pediatric patients

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

Geriatrics

Dose selection should be cautious due to potential for greater sensitivity to adverse events.

Renal Dose Adjustments

If creatinine clearance less than 30 ml/min then the dosing interval increased to every 12 hours. The maximum dose is 4 tablets per day. This drug is not recommended to the patients with creatinine clearance less than 10ml/min.

Liver impairment

Use is not recommended.

CONTRAINDICATIONS :

Hypersensitivity to the active substances in this fixed dose combination i.e. Tramadol or Paracetamol. Acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products.

This drug should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

Combination of Tramadol and Paracetamol is not recommended to those who are having severe hepatic impairment problem and epilepsy not controlled by treatment.

WARNING AND PRECAUTIONS :

The maximum dose of 8 tablets per day should not be exceeded in adults and adolescents 12 years and older. In order to avoid overdose, patients should be advised not to exceed the recommended dose and not to use any other Paracetamol or Tramadol hydrochloride containing products concurrently without the advice of a physician.

This drug is not recommended in severe renal impairment (creatinine clearance <10 ml/mm). In patients with severe hepatic impairment should not be used. The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.

Tramadol hydrochloride and Paracetamol is not recommended in severe respiratory impairment. Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

Convulsions have been reported in patients treated with Tramadol. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with this drug only if there are compelling circumstances.

Paracetamol overdosage may cause hepatic toxicity in some patients.

INTERACTION WITH DRUGS AND OTHER SUBSTANCES :

Interaction with non selective Monoamine Oxidase (MAO) Inhibitors :
Risk of serotoninergic syndrome like diarrhea, tachycardia, hyperhidrosis, trembling, confusional state and even may lead to coma.

With Selective-A MAO Inhibitors :
Extrapolation from non selective monoamine oxidase inhibitors, risk of serotoninergic syndrome.

Selective-B MAO Inhibitors :
Central excitation symptoms evocative of a serotoninergic syndrome. 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:

With Alcohol- Alcohol increases the sedative effect of opioid analgesics. Avoid intake of alcoholic drinks and of medicinal products containing alcohol while taking this medicine.

With carbamazepine and other enzyme inducers – There is risk of reduced efficacy and shorter duration due to decreased plasma concentrations of Tramadol.

With opioid agonists or antagonists - Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

Other drugs known to inhibit CYP3A4 - Some drugs like ketoconazole and erythromycin that known to inhibit CYP3A4 might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite.

Use fertility, pregnancy and lactation

Pregnancy **-** Since Tramadol hydrochloride and Paracetamol is a fixed combination of active ingredients including tramadol; it should not be used during pregnancy. There is inadequate evidence available to assess the safety of tramadol in pregnant women.

Lactation **–** Since this medicine is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding. Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Tramadol hydrochloride should not be administered during breast feeding.

Fertility **-** Post marketing survey established that Tramadol do not have effect on fertility. Moreover, animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of Tramadol and Paracetamol.

ADVERS EFFECTS :

Tramadol-

Tramadol hydrochloride may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. Postural hypotension, bradycardia and collapse may associate with Tramadol.

Psychic side-effects may occur following administration of Tramadol which vary individually depending on personality and duration of medication. These include changes in mood, changes in activity and changes in cognitive and sensorial capacity.

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur.

Paracetamol-

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. 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.

OVERDOSE :

This drug is a fixed combination of active ingredients Tramadol hydrochloride 37.5mg and Paracetamol 325mg. In case of overdose, the signs and symptoms of toxicity of Tramadol or Paracetamol or of both these active ingredients will manifest.

Overdose of Tramadol –

In case of intoxication with Tramadol, symptoms similar to those of other centrally acting analgesics like opioids are to be expected. These symptoms include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Overdose of Paracetamol –

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 with Paracetamol, 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.

Treatment of overdose*:*

If overdose is suspected with this drug then transfer the patient immediately to a specialized unit. Maintain respiratory and circulatory functions.

Prior to starting treatment overdose, 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 and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.

STORAGE :

Store Trapadol Tablet between 15 and 30 degrees C.

PRESENTATION :

Trapadol Tablet is available in 10x10’s in box.