For the use of a Registered Medical Practitioner only

℞ Tramadol Hydrochloride and Acetaminophen Tablets USP

Ifimol® T

COMPOSITION:

Each film coated tablet contains:

Tramadol Hydrochloride IP ..... 37.5 mg

Acetaminophen (Paracetamol) IP ..... 325 mg

Excipients ..... q.s.

Colours : Ferric Oxide Yellow USP-NF
(Yellow Oxide of Iron) and Titanium Dioxide IP

PHARMACEUTICAL FORM

Film Coated Tablet.

THERAPEUTIC INDICATION

It is indicated for the short-term (five days or less) management of acute pain in adults. Also, indicated for symptomatic treatment of moderate to severe pain.

DOSAGEAND ADMINI STRATION

Posology

The use of Tramadol/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.

Adults: An initial dose of two tablets of Tramadol / Paracetamol tablet is recommended or as directed by the Physician.

Additional doses can be taken as needed (not exceeding the recommended dose, equivalent to 300 mg tramadol and 2600 mg paracetamol) per day. The dosing interval should not be less than 6 hours.

Special population

Paediatricpopulation: The effective and safe use of Tramadol hydrochloride/Paracetamol has not been established in children below the age of 12 years.

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.

The usual dosages may be used, although it should be noted that in volunteers aged over 75 years the elimination half-life of tramadol was increased by 17% for lowingoral administration. 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 Tramadol/Paracetamol is not recommended in patients with severe renal failure (creatinine clearance < 10ml/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 hemodialysis 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. Because of the presence of paracetamol, Tramadol/Paracetamol tablets should not be used in patients with severe hepatic impairment.

Method of administration: For oral use only.

Tramadol/Paracetamol tablets must be swallowed whole, with a sufficient quantity of liquid and should not be crushed or chewed.

CONTRAINDICATIONS

It is contraindicated in patients with known or previous hypersensitivity to tramadol, acetaminophen, any other component of this product, or opioids.

- Acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products.
- Severe hepatic impairment.
- Epilepsy not controlled by treatment.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
- Significant respiratory depression.
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
- Tramadol/Paracetamol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

- In adults. The maximum dose (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) of 8 tablets a day of Tramadol/Paracetamol 37.5 mg/ 325 mg should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.
- In severe renal insufficiency (creatinine clearance <10 ml/min) Tramadol/Paracetamol tablet is not recommended.
- In patients with severe hepatic impairment Tramadol / Paracetamol tablet 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.
- In severe respiratory insufficiency Tramadol/Paracetamol tablet is not recommended.
- 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 tramadol-treated patients susceptible to seizures or taking other medicines that lower the seizure threshold, especially selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Tramadol/Paracetamol only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limit.
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended.

Drug dependence, tolerance and poten tial for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. 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).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse. A comprehensive patient history should be taken to document concomitant medications,

including over-the-counter medicines and medicines obtained on-line, and past and present medical and 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. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP206. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that upto 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing <side effects> of opioid toxicity even at commonly prescribed doses. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Tramadol/Paracetamol and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol/ Paracetamol concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible . The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms .

Serious Skin Reactions

Rarely, acetaminophen 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.

Risk of Use in Patients with Gastrointestinal Conditions

Tramadol/Paracetamol is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The tramadol in Tramadol/Paracetamol tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Special warnings and precautions for use

A paracetamol overdose can cause hepatic toxicity in some patients.

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

Drug withdrawal syndrome

Prior to star ting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with tramadol. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months. The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate. If women take this drug during pregnancy, there is a risk that their new born infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Important Dosage and Administration Instructions

Tramadol/Paracetamol tablets should under no circumstances be administered for longer than is strictly necessary. If repeated use or the long term treatment with Tramadol/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.

Do not exceed the recommended dose of Tramadol/Paracetamol tablets. Do not co-administer Tramadol/Paracetamol tablets with other tramadol or acetaminophen (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 with Tramadol/Paracetamol and adjust the dosage accordingly.

DRUG INTERACTIONS

Concomitant use is contraindicated with:

Non-selective MAO Inhibitors: Risk of serotoninergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

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

Selective-8 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 2 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, and pentazocine): Decrease of 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 SSRIs, SNRIs, MAO inhibitors, tricyclic antidepressants (TCAs) 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.

Sedative medicines such as benzodiazepines or related drugs:

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 effect. The dose and duration of concomitant use should be limited.

- 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 CNS 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.
- 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.
- 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 0-demethylated metabolite . The clinical importance of such an interaction has not been studied.
- Medicinal products reducing the seizure threshold, such as bupropion, serotonin reuptake inhibitors, tricyclic antidepressants and neuroleptics. Concomitant use of tramadol with these drugs can increase the risk of convulsions. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
- In a limited number of studies, the pre- or post-operative application of the antiemetic SHT3-antagonist, ondansetron, increased the requirement for tramadol in patients with post-operative pain.

USE IN SPECIFIC POPULATION

Pregnancy

Since Tramadol/Paracetamol is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

Data regarding paracetamol: A large amount of data on pregnant women indicates neither malformative, nor feta/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. 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.

Data regarding tramadol: Tramadol should not be used during pregnancy, as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Tramadol administered before or during birth, does not affect uterine contractions.

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.

Lactation

Administration to nursing women is not recommended as tramadol may be secreted in breast milk and may cause respiratory depression in the infant.

Data on paracetamol: 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.

Data on tramadol: Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Females and Males of Reproductive Potential

Infertility: 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.

Pediatric Use

The safety and effectiveness of Tramadol/Paracetamol tablets in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received tramadol. In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 206). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

- Tramadol/Paracetamol is contraindicated for all children younger than age 12 years of age.
- Tramadol/Paracetamol is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- Avoid the use of Tramadol/Paracetamol 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.

Geriatric Use

Elderly patients (65 years of age or older) may have increased sensitivity to tramadol. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Tramadol/Paracetamol slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression.

Tramadol and acetaminophen are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tramadol may cause drowsiness or dizziness, which may be enhanced by alcohol or other central nervous system (CNS) depressants. If affected, the patient should not drive or operate machinery. This medicine can impair cognitive function and can affect a patient's ability to drive safely.

UNDESIRABLE EFFECTS

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

The frequencies are defined as follows: Very common: ≥:1/10, Common: ≥:1/100 to <l/10, Uncommon: ≥:1/1000 to <1/100, Rare: ≥:1/10 000 to <1/1000, Very rare: <1/10 000, Unknown: Frequency cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders: Uncommon: palpitations, tachycardia, and arrhythmia.

Eye disorders: Rare: vision blurred, miosis, mydriasis.

Ear and labyrinth disorders: Uncommon: tinnitus.

Gastrointestinal disorders: Very common : nausea. Common : vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence. Uncommon: dysphagia, melaena.

General disorders and administration site conditions: Uncommon : chills, chest pain, drug withdrawal syndrome.

Investigations: Uncommon: transaminases increased.

Metabolism and nutrition disorders: Unknown : hypoglycaemia.

Nervous system disorders: Very common: dizziness, somnolence. Common: headache, trembling. Uncommon: involuntary muscular contractions, paraesthesia, amnesia. Rare: ataxia, convulsions, syncope, speech disorders.

Psychiatric disorders: Common: confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders. Uncommon: depression, hallucinations, nightmares. Rare: delirium. Frequency unknown: Drug dependence.

Post marketing surveillance: Very rare: abuse.

Renal and urinary disorders: Uncommon: albuminuria, micturition disorders (dysuria and urinary retention).

Respiratory, thoracic and mediastinol disorders: Uncommon: dyspnoea.

Skin and subcutaneous tissue disorders: Common: hyperhidrosis, pruritus. Uncommon: dermal reactions (e.g. rash, urticaria).

Vascular disorders: Uncommon: hypertension, hot flush.

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

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 (1/10,000 to <1/1,000): Allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) anaphylaxis. Rare cases: Changes in appetite, motor weakness, & 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 elation occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive & sensorial capacity (e.g. decision behaviour perception disorders).
- Worsening of asthma has been reported though a causal relationship has not been established.
- Symptoms of withdrawal reactions, 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.

Paracetamol

Fixed drug eruption (FOE) has been reported with 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.

Reporting of side effects or suspected adverse reaction: Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

OVERDOSE

Tramadol/Paracetamol is a fixed combination of active substances. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol and/or paracetamol or of both these active ingredients. Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms of 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 up to coma, convulsions and respiratory depression up to respiratory arrest.

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 encephalophathy, 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 specialized unit. Maintain respiratory and circulatory functions.
- Perform blood test and 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 1 or 2 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 haemofiltration. Therefore, treatment with of acute intoxication with Tramadol/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 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.

PHARMACOLOGICALPROPERTIES

Pharmacodynamic properties

The product contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake, and acetaminophen (paracetamol).

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure, non-selective agonist of the μ, 6 and K opioid receptors, with a higher affinity for μ receptors. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol causes an antitussive effect. 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. Opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the 0-demethylated metabolite Ml to μ-opioid receptors. In animal models, Ml 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 Ml 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.

Acetaminophen is a non-opioid, non-salicylate analgesic. The exact mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects. Tramadol/Paracetamol is positioned as a Class II analgesic on the WHO pain ladder and should be utilised accordingly by physicians.

Pharmacokinetic properties

Tramadol is administered in racemic form and the[-] and[+] forms of tramadol and its metabolite Ml, 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 tablet of tramadol/paracetamol (37.5 mg/325 mg), peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-) -tramadol] and 4.2 μg/ml (paracetamol) are reached after 1.8 h [(+) tramado l/(-)-tramadol] and 0.9 h (paracetamol), respectively. The mean elimination half-lives tl/2 are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol). During pharmacokinetic studies performed on healthy volunteers, after single and repeated oral administrations of Tramadol/Paracetamol, no significant clinical changes were seen in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption

Racemic tramadol is absorbed readily and almost completely after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75%. After repeated administration, the bioavailability increases and reaches approximately 90%.

After the administration of Tramadol/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. Oral administration of Tramadol/Paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol; therefore, Tramadol/Paracetamol can be taken independently of meal times.

Distribution

Tramadol has a high tissue affinity (Vd,β=c203 ±40 I). 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 0.91/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism

Tramadol is metabolised extensively after oral administration. About 30% of the dose is excreted, unchanged, in urine as unchanged drug, while 60% is excreted as metabolites.

Tramadol is metabolised through 0-demethylation (catalysed by the enzyme CYP2D6) of the metabolite Ml, and through N-demethylation (catalysed by CYP3A) of the metabolite M2. Ml is also metabolised by N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of Ml is 7 hours. The metabolite, Ml, has analgesic properties and is more potent than the parent drug. The plasma concentrations of Ml are several fold lower than those of tramadol, and the contribution to the clinical effect is unlikely to change with multiple doses.

Paracetamol is principally metabolised mainly in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses that are higher than the therapeutic dose. A small fraction (less than 4%) is metabolised by the cytochrome, P450, to an active intermediate product (N-acetyl benzoquinoneimine), which, under normal conditions of use, is readily detoxified by reduced glutathione and excreted in urine after conjugation tocysteine and mercapturicacid. However, in cases of massive overdose, the quantity of this metabolite is increased.

Elimination

Tramadol and its metabolites are cleared mainly by the kidneys. The half-life of paracetamol is about 2 to 3 hours in adults. It is shorter in children and slightly longer in newborns and cirrhotic patients. Paracetamol is mainly eliminated by the dose-dependent formation of glucoro-conjugated and sulpho-conjugated derivatives. Less than 9% of paracetamol is excreted, unchanged, in urine. In renal insufficiency, the half-life of both compounds is prolonged.

INCOMPATIBILITY

None stated.

PACKING INFORMATION

20x15 Tablets (Blister Pack)

SHELF LIFE

Refer to carton

STORAGE INSTRUCTIONS

Store protected from light & moisture, at a temperatures between 20°C - 25°C.

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
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Note: This prescribing information is applicable for India Market only