TRAMAL PLUS
(Tramadol HCl + Paracetamol)

37.5mg + 325mg

Tablet

WARNING

ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING 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

Addiction, Abuse, and Misuse: tramadol hydrochloride and acetaminophen exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tramadol hydrochloride and acetaminophen, and monitor all patients regularly for the development of these behaviors and conditions.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS): To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Healthcare providers are strongly encouraged to counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, emphasize to patients and their caregivers.

Life-Threatening Respiratory Depression: Serious, life-threatening, or fatal respiratory depression may occur with use of tramadol hydrochloride and acetaminophen. Monitor for respiratory depression, especially during initiation of tramadol hydrochloride and acetaminophen or following a dose increase.

Accidental Ingestion: Accidental ingestion of even one dose of tramadol hydrochloride and acetaminophen, especially by children, can result in a fatal overdose of tramadol. Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-Threatening Respiratory Depression in Children Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases occurred following tonsillectomy and/or adenoidectomy, and in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. tramadol hydrochloride and acetaminophen is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Avoid the use of tramadol hydrochloride and acetaminophen 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.

Neonatal Opioid Withdrawal Syndrome: Prolonged use of tramadol hydrochloride and acetaminophen during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. 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

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes: The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol hydrochloride and acetaminophen requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1

Hepatotoxicity: Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants: Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death

Reserve concomitant prescribing of tramadol hydrochloride and acetaminophen and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

COMPOSITION

Each film-coated tablet contains:
Tramadol HCl…… 37.5mg
Paracetamol……325mg

THERAPEUTIC INDICATIONS

Tramadol hydrochloride/Paracetamol tablets are 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 AND 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 hydrochloride 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.

Paediatric 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

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 requirements.

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 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 crushed or chewed.

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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

- The maximum dose of 8 tablets of Tramadol hydrochloride/Paracetamol should not be exceeded in adults and adolescents 12 years and older. 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 impairment (creatinine clearance <10 ml/min), Tramadol hydrochloride/Paracetamol is not recommended.

- In patients with severe hepatic impairment Tramadol hydrochloride/Paracetamol 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 impairment, Tramadol hydrochloride/Paracetamol 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 medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Tramadol hydrochloride/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.

Precautions for use

Concomitant use of Tramadol hydrochloride/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 hydrochloride/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.

Tolerance, physical and psychological dependence may develop, even at therapeutic doses, especially after long-term use. The clinical need for analgesic treatment should be reviewed regularly. In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period and under medical supervision.

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 centre or the respiratory function, or with an increased intracranial pressure.

Paracetamol overdosage 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. When a patient no longer requires therapy with opioid, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

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

CYP2D6 metabolism

Tramadol is metabolized by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metabolizer 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. Estimates of prevalence of ultra-rapid metabolizers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnea, led to rare, but life-threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function

Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

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-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.

- 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.

- 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.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Since Tramadol hydrochloride/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 feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

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 contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

Breast-feeding

Since Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients including tramadol, it should not be used more than once during breast feeding or alternatively, breast-feeding should be discontinued during treatment with tramadol.

Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data on paracetamol does not contraindicate it for breast feeding by women using single ingredient medicinal products containing only paracetamol.

Data regarding 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.

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tramadol hydrochloride may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

ADVERSE DRUG REACTIONS

Undesirable effects that may occur during treatment with Tramadol hydrochloride/Paracetamol are classified into the following groups in order of frequency:

- very common (≥1/10)

- common (≥1/100 to <1/10)

- uncommon (≥1/1,000 to <1/100)

- rare (≥1/10,000 to <1/1,000)

- very rare (<1/10,000)

- not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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% of the patients.

Frequency of undesirable effects listed by individual organ systems:

	Very common	Common	Uncommon	Rare	Very rare	Unknown
Metabolism and nutrition disorders						hypoglycemia
Psychiatric disorders		confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders	depression, hallucinations, nightmares	delirium, drug dependence	abuse*	
Nervous system disorders	dizziness, somnolence	headache, trembling	involuntary muscular contractions, paraesthesia, amnesia	ataxia, convulsions, syncope speech disorders		
Eye disorders				miosis, mydriasis blurred vision		
Ear and labyrinth disorders			tinnitus			
Cardiac disorders			palpitations, tachycardia, arrythmia			
Vascular disorders			hypertension, hot flush			
Respiratory, thoracic and mediastinal disorders			dyspnea			
Gastrointestinal disorders	nausea	vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence	dysphagia, melaena.			
Skin and subcutaneous tissue disorders		hyperhidrosis, pruritus	dermal reactions (e.g. rash, urticaria)			
Renal and urinary disorders			albuminuria, micturition disorders (dysuria and urinary retention).			
General disorders and administration site conditions			chills, chest pain			
Investigations			transaminases increase			

*Reported in post marketing surveillance.

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:

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. dyspnea, 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 elation occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behavior 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

- 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 suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pv@searlecompany.com

OVERDOSE

Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

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 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 specialized 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 hemodialysis or hemofiltration. Therefore, treatment of acute intoxication with Tramadol hydrochloride/Paracetamol with hemodialysis or hemofiltration 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 ≥150 mg/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 N-acetylcysteine (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 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, opioids in combination with non-opioid analgesics, tramadol and paracetamol, ATC code: N02AJ13.

Analgesics

Tramadol is an atypical opioid analgesic that acts on the central nervous system. Tramadol is pure nonselective agonists of the μ, 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 antitussive 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.

Mechanism 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 utilized accordingly by the physician.

Pharmacokinetic properties

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/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 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 $t_{1/2}$ 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 clinically 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 mealtimes.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}$=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 relatively 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 metabolized through *O*-demethylation (catalyzed by the enzyme CYP2D6) to the metabolite M1, and through *N*-demethylation (catalyzed by CYP3A) to the metabolite M2. M1 is further metabolized 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.

PRECLINICAL SAFETY DATA

No preclinical study has been performed with the fixed combination (*tramadol and paracetamol*) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the *combination tramadol/paracetamol.*

The *combination tramadol/paracetamol* has proven to be embryotoxic and fetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the fetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the fetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for *tramadol* in man.

Results of carcinogenicity tests do not suggest a potential risk of *tramadol* for man.

Animal studies with *tramadol* revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. *Tramadol* crosses the placenta. No effect on fertility has been observed after oral administration of tramadol up to doses of 50 mg/kg in the male rat and 75 mg/kg in the female rat.

Extensive investigations showed no evidence of a relevant genotoxic risk of *paracetamol* at therapeutic (i.e. non-toxic) doses.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of *paracetamol*.

Conventional studies using the currently accepted standards for the evaluation of *paracetamol* toxicity to reproduction and development are not available.

PRESENTATION

Tramal Plus Tablets are available in alu-alu blister pack of 10 Tablets.

INSTRUCTIONS

-To be sold on the prescription of a registered medical practitioner only.

-Protect from sunlight, moisture and heat.

-Store below 30°C.

-Keep all medicines out of sight and reach of children.

REGISTRATION NUMBER

Tramal Plus : 077129

Manufacturing Licence No: 000647

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mfg. U.S.P. Specs. Manufactured by:

The Searle Company Limited,

32-Km, Multan Road, Lahore-Pakistan.

DATE OF PUBLICATION OF THE PACKAGE INSERT

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