PATRIOT
Pharmaceuticals Corp.

Tramadol HCl + Paracetamol

TDL® Plus
37.5mg/325mg Film-Coated Tablet
Opioid Analgesic

Formulation:
Each tablet contains:
Tramadol hydrochloride.....37.5mg
Paracetamol.....325mg

PROPERTIES
Pharmacodynamics
Tramadol is a centrally acting analgesic compound. At least two complementary mechanisms appear applicable, binding of parent and M1 metabolite to u-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Paracetamol is another centrally acting analgesic. The exact site and mechanisms of its analgesic action is not clearly defined when evaluated in a standard animal model. The combination of Tramadol and paracetamol exhibited a synergistic effect.

Pharmacokinetics
General
Tramadol is administered as a racemic and both the [-] and [+] forms of both Tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma Tramadol and paracetamol following oral administration of one Tramadol + paracetamol tablet are shown in table 1. Tramadol has a slower absorption and longer half-life when compared to paracetamol.
After a single oral dose of one Tramadol + paracetamol combination tablet (37.5mg/325mg), peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2ug/mL (paracetamol) are reached after 1.8h [(+)-tramadol/(-)-tramadol] and 0.9h (paracetamol), respectively. Mean elimination half lives t1/2 are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol). Single and multiple dose pharmacokinetics studies of Tramadol + paracetamol in volunteers showed no significant drug interactions between Tramadol and paracetamol.

Table 1: Summary of mean (±SD) Pharmacokinetic parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and paracetamol following a Single oral dose of One Tramadol + Paracetamol Combination Tablet (37.5mg/325mg) in volunteers.

Parameter	(+)-Tramadol	(-)-Tramadol	(+)-M1	-(-)M1	Paracetamol
Cmax (ng/mL)	64.3 (9.3)	55.5 (8.1)	10.9 (5.7)	12.8 (4.2)	4.2 (0.8)
t max (h)	1.8 (0.6)	1.8 (0.7)	2.1 (0.7)	2.2 (0.7)	0.9 (0.7)
CL/F (mL/min)	588 (226)	736 (244)	- -	- -	365 (84)
t½ (h)	5.1 (1.4)	4.7 (1.2)	7.8 (3.0)	6.2 (1.6)	2.5 (0.6)

* for paracetamol, Cmax measures as ug/mL

Absorption
Tramadol hydrochloride has a mean absolute bio availability of approximately 75% following administration of a single 100mg oral dose of Tramadol tablets. The mean peak plasma concentration of racemic Tramadol and M1 after administration of two Tramadol + paracetamol tablets occurs at approximately two and three hours, respectively, post-dose in healthy adults.
Oral absorption of paracetamol following administration of Tramadol + paracetamol is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of paracetamol occur within 1 hour and are not affected by co-administration with tramadol.
Food effects
The 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, so that Tramadol + paracetamol can be taken independently of meal times.
Distribution
The volume of distribution was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100mg intravenous dose. The binding of Tramadol to human plasma proteins is approximately 20%.
Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9L/kg.
A relative small portion (~20%) of paracetamol is bound to plasma protein.
Metabolism
Plasma concentration profiles of Tramadol and its M1 metabolite measures following dosing of Tramadol + paracetamol in volunteers showed no significant change compared to dosing with Tramadol alone.
Approximately 30% of the dose is excreted in the urine as unchanged drugs, 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. Tramadol is extensively metabolized by a number of pathways, including CYP2D5.
Paracetamol is primarily metabolized in the liver by first order kinetics and involves three principle separate pathways:
A.) Conjugation with Glucuronide
B.) Conjugation with Sulfate; and
C.) Oxidation via cytochrome, P450 enzyme pathways:
Elimination
Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half lives of racemic Tramadol and M1 are approximately six and seven hours, respectively. The plasma elimination half life of racemic tramadol has increased from approximately six hours to seven hours upon multiple dosing of Tramadol + paracetamol. 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 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.
Preclinical Safety Data
Tramadol +Paracetamol combination
There are no animal or laboratory studies on the combination product (Tramadol and Paracetamol) to evaluate carcinogenesis, mutagenesis or impairment of fertility. No drug related teratogenic effects were observed in the progeny of rats treated orally with the combination of Tramadol and paracetamol. The Tramadol + paracetamol combination product was shown to be embryo toxic and fetotoxic in rats at a maternally toxic dose (50/434 mg/kg Tramadol + Paracetamol) 8.3 times the maximum human dose but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. Lower and less severe maternally toxic dosages (10/87 and 25/217 mg/kg Tramadol + Paracetamol) did not produce embryo of fetal toxicity.
Tramadol Hydrochloride
Carcinogenicity/Mutagenicity
A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice (dosing orally up to 30mg/kg for approximately two years, although the study was not done with the maximum tolerated dose). This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study. Tramadol was not mutagenic in the following assays: Ames Salmonella microsome activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration tests in Chinese hamster, and bone marrow micro nucleus tests in mice and Chinese hamsters.
Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micro nucleus test in rats. Overall, the weight of evidence from these tests indicates that the Tramadol does not pose a genotoxic risk to humans.
Impairment of Fertility/ effect on reproduction
No effects on fertility were observed for Tramadol at oral dose levels up to 50mg/kg in male rats and 75mg/kg in female rats. Tramadol was evaluated in peri and post natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80mg/kg (6 to 10 times the maximum human dose). No toxicity was observed at all dose levels of Tramadol in this study, but effects on progeny were evident only at higher dose levels where maternal toxicity was more severe.

INDICATIONS
Tramadol + Paracetamol is indicated for the management of moderate to severe pain.

CONTRAINDICATIONS
Tramadol + paracetamol should not be administered to patients who have previously demonstrated hypersensitivity to Tramadol, Paracetamol and any other component of this product or opioids. It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psycho tropic drugs.

SPECIAL WARNING AND SPECIAL PRECAUTIONS FOR USE
Seizures
Seizures have been reported in patients receiving Tramadol within the recommended dosage range. Spontaneous post marketing reports indicate that the seizures risk is increased with the doses of Tramadol above the recommended range. Concomitant use of Tramadol increases the seizures risk in patients taking : selective serotonin reuptake inhibitors (SSRI) antidepressants or anorectics, tricyclic antidepressants (TCAs) and other tricyclic compounds (e.g., Cyclobenzaprine, promethazine, etc.), or opioids.
Administration of Tramadol may enhance the seizures risk in patients taking MAO inhibitors, neuroleptics or other drugs that reduce the seizure's threshold. Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol, and drug withdrawal, CNS infections). In Tramadol overdose, naloxone administration may increase the risk of seizures.
Anaphylactoid Reactions
Patients with a history of Anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive Tramadol + Paracetamol.
Respiratory Depression
Administer Tramadol + Paracetamol cautiously in patients at risk of respiratory depression. When large doses of Tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.
Use with CNS Depressants
Tramadol + Paracetamol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents,Phenothiazines tranquilizers or sedative hypnotics.
Increased Intra-cranial Pressure or Head Trauma
Tramadol + Paracetamol should be used with the caution in patients with increased intra- cranial pressure or head injury.
Use with Alcohol
Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use.
Withdrawal
Withdrawal symptoms may occur if Tramadol + Paracetamol is discontinued abruptly. Pain attack, severe anxiety, hallucinations, paresthesia, tinnitus, and unusual CNS symptoms have also been rarely reported with abrupt discontinuation of Tramadol hydrochloride. Clinical experience suggest that the withdrawal symptoms may be received by tapering the medication.
Use with MAO Inhibitors and Serotonin Reuptake Inhibitors
Use Tramadol + Paracetamol with great caution in patients taking monoamine oxidase inhibitors. Concomitant use of Tramadol with the MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.
Use in Renal Disease
Tramadol + Paracetamol has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30mL/min, it is recommended that the dosing interval of Tramadol + Paracetamol be increased, but not to exceed 2 tablets every 12 hours.
Use in Hepatic Diseases
The use of Tramadol + Paracetamol in patients with severe hepatic impairment is not recommended.
Serious Skin Reactions
Such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving Paracetamol
General Precautions
The recommended dose of Tramadol + Paracetamol should not be exceeded.
Tramadol + Paracetamol should not be co-administered with other Tramadol or Paracetamol-containing products.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND FORMS OF INTERACTIONS.
Use of MAO Inhibitors and Serotonin Reuptake Inhibitors
Interaction with MAO Inhibitors has been reported for some centrally-acting drugs. **(SEE SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE)** - Use with MAO inhibitors and Serotonin Reuptake Inhibitors.
Use with Carbamazepine
Concomitant administration of Tramadol Hydrochloride and Carbamazepine causes a significant increase in Tramadol metabolism. Patients taking Carbamazepine may have a significantly reduced analgesic effect from the Tramadol component of Tramadol + Paracetamol.
Use with Quinidine
Tramadol is metabolized to M1 by CYP2D6. Concomitant administration of quinidine and tramadol results in increased concentrations of Tramadol. The clinical consequences of these findings are unknown.

Use with Warfarin-like Compounds
As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol + Paracetamol and these agents are administered concurrently, due to reports of increased international normalized ratio (INR) in some patients.
Use with Inhibitors of CYP2D6
In-vitro interaction studies in human liver microsome indicate that concomitant administration with inhibitors of CYP2D6 such as Fluoxetine, Paroxetine, and Amitriptyline could result in some inhibition of the metabolism of Tramadol.
Use with Cimetidine
Concomitant administration of Tramadol + Paracetamol and Cimetidine has not been studied. Concomitant administration of Tramadol and Cimetidine does not result in clinically significant changes in Tramadol pharmacokinetics.

PREGNANCY AND LACTATION
Tramadol has been shown to cross placenta.
There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established, Tramadol + Paracetamol is not recommended for nursing mothers because its safety in infants and newborns has not been studied.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Tramadol + Paracetamol may impair mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery.

DOSAGE AND ADMINISTRATION
Unless otherwise prescribed, Tramadol + Paracetamol should be administered as follows:

Adult and Children over 16 years
The maximum single dose of Tramadol + Paracetamol is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.
Tramadol + Paracetamol can be administered without regard to food.
Pediatric (children below 16 years)
The safety and effectiveness of Tramadol + Paracetamol has not been established in pediatric population.
Elderly (Geriatric)
No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥ 65 years of age and younger subjects.

ADVERSE REACTIONS
The most frequently reported events were in the Central Nervous System and gastrointestinal system. The most common reported events were nausea, dizziness and somnolence. In addition, the following effects have been frequently observed, though the frequency is generally lower :
Body as whole - asthenia, fatigue, hot flushes;
Central and Peripheral Nervous system - headache, tremor;
Gastrointestinal system - abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, vomiting;
Psychiatric disorders - anorexia, anxiety, confusion, euphoria, insomnia, nervousness;
Skin and appendages - pruritus, rash, increased sweating;
Uncommon reported clinically significant adverse experience with at least a possible causal link to Tramadol + Paracetamol include :
Body as whole - chest pain, rigors, syncope, withdrawal syndrome;
Cardiovascular disorders - hypertension, aggravated hypertension, hypotension;
Central And Peripheral Nervous system - ataxia, convulsion, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paresthesia, stupor, vertigo;
Gastrointestinal system - dysphagia, melena, tongue edema;
Hearing and vestibular disorders - tinnitus
Heart rate and Rhythm disorders - arrhythmia, palpitation, tachycardia;
Liver and biliary system - liver test abnormalities;
Metabolic and nutritional disorder - weight decrease
Psychiatric disorders - amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking
Red blood cell disorders - anemia
Respiratory system - dyspnea;
Urinary system - albuminuria, micturition disorder, oliguria, urinary retention
Vision disorders - abnormal vision
Other clinically significant adverse experience previously reported in clinical trials or post-marketing report with Tramadol hydrochloride.
Other events which have been reported with the use of Tramadol products include :
Orthostatic hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens Johnson Syndrome/ TENS), cognitive dysfunction, suicidal tendency, and hepatitis. Reported laboratory abnormalities included elevated creatinine. Serotonin syndrome (whose symptoms may include fever, excitation, shivering, and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRI's and MAO inhibitors. Post marketing surveillance of Tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
Other clinically significant adverse experience previously reported in clinical trials or post-marketing report with Paracetamol.
Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally controlled by discontinuation of the drug, and, when necessary, symptomatic treatment. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time was not changed.

OVERDOSAGE
Tramadol + Paracetamol is a combination product. The clinical presentation of overdose may include the signs and symptoms of Tramadol toxicity, paracetamol toxicity or both. The initial symptoms of Tramadol overdosage may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following a paracetamol overdose may include : gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis.
Human experience
Tramadol
Serious potential consequences of overdosage of the Tramadol component are respiratory depression, lethargy, coma seizure, cardiac arrest and death.
Paracetamol
Paracetamol in a massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic overdosage may include : gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis.
Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Treatment
A single or multiple overdose with Tramadol + Paracetamol may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended. While naloxone will reverse some, but not all, symptoms caused by overdosage with Tramadol, the risk of seizures is also increased with Naloxone administration. Based on experience with Tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period. In treating an over dosage of Tramadol + Paracetamol, primary attention should be given to maintaining adequate ventilation along the general supportive treatment. Measures should be taken to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cartharic might be included with alternate doses as required. Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed on an unconscious patient and when necessary to provide assisted respiration. In adult and pediatric patients, any individual presenting with an unknown amount of paracetamol ingested or with a questionable or unreliable history about the time of ingestion should have a plasma paracetamol level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated paracetamol ingestion exceeds 7.5 to 10grams for adults and adolescents or 150mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

Availability:
PVC/Alu Blister Pack x 10's; (Box of 50's, 100's)

Storage:
Store at temperatures not exceeding 30°C

Caution:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
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