Front

Tramadol Hydrochloride / Paracetamol

CETODOL™

37.5 mg / 325 mg Tablet

ANALGESIC

PRODUCT NAME
Tramadol Hydrochloride & Paracetamol

DOSAGE FORM AND STRENGTH:
Film Coated Tablets, 37.5 mg/ 325 mg

PHARMACOLOGIC CATEGORY:
ANALGESIC

PRODUCT DESCRIPTION:
Light green coloured, oval shaped film-coated tablets.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Tramadol Hydrochloride BP ..... 37.5 mg
Paracetamol BP ..... 325 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:
Tramadol Hydrochloride is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than Tramadol Hydrochloride 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 Hydrochloride and M1 to human analgesia is dependent upon the plasma concentrations of each compound. Tramadol Hydrochloride has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. Apart from analgesia, Tramadol Hydrochloride) administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.
Acetaminophen is a non-opiate, non-salicylate analgesic.

Pharmacokinetics:
Absorption: The absolute bioavailability of Tramadol Hydrochloride tablets has not been determined Tramadol Hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of Tramadol & Paracetamol tablets. The mean peak plasma concentration of racemic Tramadol Hydrochloride and M1 after administration of two Tramadol & Paracetamol tablets occurs at approximately two and three hours, respectively, post-dose. Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Oral absorption of acetaminophen following administration of Tramadol & Paracetamol occurs primarily in the small intestine.
Food Effects: When Tramadol & Paracetamol was administered with food; the time to peak plasma concentration was delayed for approximately 35 minutes for Tramadol & Paracetamol and almost one hour for acetaminophen. However, peak plasma concentration or the extent of absorption of either Tramadol Hydrochloride or acetaminophen was not affected. The clinical significance of this difference is unknown.
Distribution: The volume of distribution of Tramadol Hydrochloride was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of Tramadol Hydrochloride to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 μg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range. Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.
Metabolism: Following oral administration, Tramadol & Paracetamol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N - and O- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (O - desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of Tramadol Hydrochloride were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of Tramadol Hydrochloride) to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure and serotonin syndrome. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:
a) Conjugation with glucuronide;
b) Conjugation with sulfate; and
c) Oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.
Elimination: Tramadol Hydrochloride is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic Tramadol Hydrochloride and M1 are approximately 5–6 and 7 hours, respectively, after administration of Tramadol & Paracetamol. The apparent plasma elimination half-life of racemic Tramadol Hydrochloride increased to 7–9 hours upon multiple dosing of Tramadol & Paracetamol. The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

INDICATIONS:
Tramadol & Paracetamol indicated for management of moderate to severe pain.

DOSAGE AND MODE / ROUTE OF ADMINISTRATION:
Unless otherwise prescribed, Tramadol & Paracetamol should be administered as follows:
Adults and Children >16 years: Maximum Single Dose: 1-2 tabs every 4-6 hrs as needed for pain relief up to a maximum of 8 tabs/day.
Children <16 years: The safety and effectiveness of Tramadol & Paracetamol has not been established in the pediatric population.
Elderly: No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥65 years of age and younger subjects. Tramadol & Paracetamol can be administered without regard to food.

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)
Patients who have previously demonstrated hypersensitivity to tramadol, paracetamol and any other component of Tramadol & Paracetamol or opioids. It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally-acting analgesics, opioids or psychotropic drugs.

PRECAUTIONS & WARNINGS:
Seizures: Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure 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 seizure risk in patients taking: MAO inhibitors, neuroleptics or other drugs that reduce the seizure 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 (e.g., head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.
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 for respiratory depression. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as an 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 e.g., alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics.
Increased Intracranial Pressure or Head Trauma: Tramadol & Paracetamol should be used with caution in patients with increased intracranial pressure or head injury.
Use in Opioid-Dependent Patients: Tramadol & Paracetamol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids.
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. Panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus and unusual CNS symptoms have also been rarely reported with abrupt discontinuation of tramadol HCl. Clinical experience suggests that withdrawal symptoms may be relieved 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

Size: 210 x 240 mm

with MAO inhibitors or SSRIs 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 <30 mL/min, it is recommended that the dosing interval of Tramadol & Paracetamol be increased not to exceed 2 tablets every 12 hrs.
Use in Hepatic Disease: The use of Tramadol & Paracetamol in patients with severe hepatic impairment is not recommended.
General: The recommended dose of Tramadol & Paracetamol should not be exceeded. Tramadol & Paracetamol should not be co-administered with other tramadol or paracetamol-containing products.
Effects on the Ability to Drive or Operate Machinery: Tramadol & Paracetamol may impair mental and physical abilities required for the performance of potentially hazardous tasks e.g., driving a car or operating machinery.

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

INTERACTIONS:
Use with MAO inhibitors and SSRIs: Interaction with MAO inhibitors have been reported for some centrally-acting drugs (see Precautions).
Use with Carbamazepine: Concomitant administration of tramadol HCl 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 microsomes indicate that concomitant administration with inhibitors of CYP2D6 e.g. 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.

ADVERSE EFFECTS:
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 a 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 experiences with at least a possible causal link to tramadol + paracetamol include:
Body as a Whole: Chest pain, rigors, syncope, withdrawal syndrome.
Cardiovascular Disorders: Hypertension, aggravated hypertension, hypotension.
Central and Peripheral Nervous System: Ataxia, convulsions, 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 Disorders: Decreased weight.
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 Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Tramadol HCl: Other events which have been reported with the use of tramadol products include: Orthostatic hypotension, hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, suicidal tendency and hepatitis. Reported laboratory abnormalities include 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 e.g., SSRIs and MAO inhibitors. Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
Other Clinically Significant Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports 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 hypoprothrombinaemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

OVERDOSAGE AND TREATMENT:
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 over dosage may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hrs following a paracetamol overdose may include: Gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.
Human Experience: Tramadol: Serious potential consequences of over dosage of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death.
Paracetamol: Paracetamol in massive over dosage may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic over dosage may include: Gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48-72 hrs post-ingestion.
Treatment: A single or multiple over doses of 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 over dosage 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 <7% of the administered dose in a 4-hr dialysis period.
In treating an over dosage of tramadol + paracetamol, primary attention should be given to maintaining adequate ventilation along with 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 (1 g/kg) should follow gastric emptying. The 1st dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic 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 as indicated. A cuffed endotracheal tube should be inserted before gastric lavage of the 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 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 7.5-10 g for adults and adolescents or 150 mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Film Coated Tablets, Alu/PVDC Blister Pack of 10's (Box of 50's and 100's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):
Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:
Marketing Authorization Holder
Brown & Burk Philippines Inc.
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines.

NAME AND ADDRESS OF MANUFACTURER:
MICRO LABS LIMITED-Unit III
R.S. No. 63/3 & 4,
Thiruvandar Koil,
Puducherry - 605102. INDIA.

CAUTION STATEMENT:
FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION**.**

ADR REPORTING STATEMENT:
"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sigh of Adverse Drug Reaction.

REGISTRATION NUMBER:
DRP-932

DATE OF FIRST AUTHORIZATION:
March 2013

DATE OF REVISION OF PACKAGE INSERT:
Jan. 2018

EXG-ML05I-0012/D

MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Cetodol	Colours Used BLACK
2	Strength	37.5 mg & 325 mg	
3	Component	Leaflet	
4	Category	Export - Philippines	
5	Dimension	210 x 240 mm	
6	Artwork Code	EXG-ML05I-0012/D	
7	Pharma Code	N/A	
8	Reason for Change	Size & New Regulation text	

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	05-08-2019					