Tramadol hydrochloride + Paracetamol

Algesia®

37.5 mg / 325 mg film-coated TABLET
ANALGESIC

FORMULATION
Each film-coated tablet contains:
Tramadol hydrochloride……..37.5 mg
Paracetamol……..325 mg

PRODUCT DESCRIPTION
Tramadol hydrochloride 37.5 mg + paracetamol 325 mg (Algesia) Tablet is a blue, film-coated, biconvex, elliptical tablet bisected on one side and plain on the other side

CLINICAL PHARMACOLOGY
Pharmacodynamics
Tramadol is a synthetic opioid analgesic. Its exact mechanism of action is unknown but its analgesic effect appears to be produced via the following mechanisms: (1) the affinity of M1, tramadol's major metabolite, for the μ opioid receptor (2) the inhibition of the reuptake of serotonin and noradrenaline.

Paracetamol has analgesic and antipyretic properties with weak anti-inflammatory activity. The mechanism behind its therapeutic effects has not been clearly explained although recent studies propose that paracetamol inhibits the peroxidase portion of cyclooxygenase, specifically targeting cyclooxygenase-3 (COX-3) enzyme, which is mainly responsible for the synthesis of prostaglandins in the brain cortex.

The tramadol + paracetamol combination presents an opportunity to improve the spectrum of analgesic activity and reduce opioid dosage. Studies have shown that tramadol given at subtherapeutic doses (25% less than the recommended dose) together with paracetamol at a fixed ratio of 1:9 can provide the same analgesic effect produced by equianalgesic doses (50 mg) of tramadol alone. The dose reduction markedly diminished the troublesome dose-related adverse effects of tramadol (nausea, dizziness, somnolence, constipation, and vomiting) and improved tolerability.

Pharmacokinetics
After a single oral dose of tramadol 37.5 mg + paracetamol 325 mg combination tablet, peak plasma concentrations (C_{max}) of both tramadol enantiomers were 64.3 ng/mL [(+)-tramadol] and 55.5 ng/mL [(-)-tramadol]. These concentrations were achieved after 1.8 hours. Peak plasma concentration of paracetamol achieved after 0.9 hour was 4.2 mcg/mL. The mean elimination half-lives ($t_{1/2}$) of both tramadol enantiomers were 5.1 hours [(+)-tramadol] and 4.7 hours [(-)-tramadol] and 2.5 hours for paracetamol.

Tramadol is well absorbed with mean absolute bioavailability of approximately 75% after a single oral 100 mg dose. Peak concentrations of tramadol and the M1 metabolite occur after 2 and 3 hours, respectively.

Paracetamol is rapidly and completely absorbed in the small intestine via passive diffusion. Peak plasma concentrations are achieved within 0.4 to 1 hour. A fatty meal may delay absorption but does not affect extent of absorption.

Tramadol has high tissue affinity with a volume of distribution of 2.6 and 2.9 L/kg in male and female subjects, respectively, after oral administration. Its affinity for plasma proteins is approximately 20% and saturation occurs at doses beyond the therapeutic range.

Paracetamol is evenly distributed throughout most body fluids, but not in fatty tissue. Volume of distribution is approximately 0.9 L/kg. Its affinity for plasma proteins is low (approximately 10%-25%), and practically does not displace other drugs which are highly protein-bound.

Tramadol and its metabolites undergo extensive hepatic metabolism via the CYP 2D6 and CYP 3A4 pathways and conjugation of the parent drug and its metabolites. Most of the drug is excreted in the urine as metabolites (approximately 60%) and the remaining drug fraction is excreted in its unchanged form.

Paracetamol metabolism follows first-order kinetics, and primary metabolic pathways involve conjugation with glucuronide and sulfate and oxidation via the cytochrome P-450 mixed-function oxidase pathway. In adults, most of the drug fraction is transformed into the inactive glucuronide salt, and the remainder is conjugated with sulfate.

Tramadol is cleared from the circulation via renal excretion. The plasma elimination half-lives of racemic tramadol and M1 are approximately 6 and 7 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately 7 to 9 hours upon multiple dosing of tramadol + paracetamol.

Paracetamol has a plasma elimination half-life that ranges from 2 to 3 hours in adults but this may be prolonged in patients with liver disease. It is mainly excreted in the urine in its glucuronide or sulfate form, and less than 9% is excreted unchanged.

INDICATION
- For the short-term (5 days or less) management of acute pain.

DOSAGE AND ADMINISTRATION
Tramadol + paracetamol can be administered with or without food and is for oral use only.

Adults and children over 16 years old:

Orally, 1 to 2 tablets every 4 to 6 hours, as needed for pain relief, or, as prescribed by a physician.

Maximum: 8 tablets per day.

Patients with a creatinine clearance of less than 30 mL/min:

It is recommended that the dosing interval of tramadol + paracetamol be increased not to exceed 75 mg of tramadol and 650 mg of paracetamol (2 tablets) every 12 hours.

CONTRAINDICATIONS
- Hypersensitivity to tramadol, paracetamol, other opioids, or any component of the product.
- In conditions where opioids are contraindicated, such as in acute intoxication with the following substances: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids, or psychotropic drugs, tramadol + paracetamol may worsen Central Nervous System (CNS) and respiratory depression in these patients.

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Algesia contains tramadol hydrochloride and paracetamol. Paracetamol 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 paracetamol at doses that exceed 4,000 mg (4 g) per day, and often involve more than one paracetamol-containing product.

TRAMADOL:
Seizure Risk
Seizures have been reported in patients receiving tramadol even within the recommended dose range. Seizure risk is increased with tramadol doses above the recommended range. Seizures can also occur after the first dose. Concomitant use of tramadol increases seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics)**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzapine, promethazine, etc.)**
- **MAO inhibitors**
- **Antipsychotics or neuroleptics (e.g., haloperidol, droperidol, thioridazine)**
- **Other drugs that reduce seizure threshold**
- **Other opioids**

Tramadol use may also increase the risk of convulsions 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). Administration of naloxone for tramadol overdose may increase the risk of seizure.

Serotonin Syndrome Risk
Potentially life-threatening serotonin syndrome may occur with the use of tramadol-containing products even within the recommended dose. This may occur particularly with the concomitant use of:

- **Serotonergic drugs such as serotonin-norepinephrine reuptake inhibitors (SNRIs), SSRIs, TCAs, MAOIs, and triptans (e.g., sumatriptan, naratriptan, rizatriptan)**
- **Drugs that impair metabolism of serotonin (including MAOIs)**
- **Drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors)**

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordiation) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Hypersensitivity/Anaphylaxis
Serious and rarely fatal anaphylactic reactions have been reported in patients on tramadol therapy. These events occur often following the first dose. Patients with a history of anaphylactoid reactions to codeine or other opioids may be at an increased risk and should therefore not receive tramadol + paracetamol.

Alcohol and Drugs of Abuse
Tramadol may be expected to have additive effects when used concomitantly with alcohol, other opioids or illicit drugs that cause CNS depression.

Effects on Ability to Drive and Use Machines
Tramadol may impair mental or physical abilities required to perform potentially hazardous tasks such as driving and operating machinery.

PARACETAMOL:
Hepatotoxicity (see Boxed Warning)
The excessive intake of paracetamol may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other paracetamol-containing products.

The risk of acute liver failure is higher in persons with an underlying liver disease and those who ingest alcohol while taking paracetamol.

Patients should be instructed to look for paracetamol or acetaminophen or APAP on package labels and not to use more than one product that contains paracetamol. Medical attention should be sought immediately upon ingestion of more than 4,000 mg of paracetamol per day, even if they feel well.

Use with other Paracetamol-Containing Products

Do not use concomitantly with other paracetamol-containing products due to the potential for paracetamol hepatotoxicity at doses higher than the recommended dose.

TRAMADOL + PARACETAMOL:
Suicide Risk
Do not prescribe tramadol + paracetamol to patients who are suicidal or addiction prone. Prescribe tramadol + paracetamol with caution in patients who are:

- **Taking tranquilizers or antidepressant drugs**
- **Consuming excessive amounts of alcohol**
- **Suffering from emotional disturbance or depression**

The cautious prescribing of tramadol is essential for the safe use of this drug. Consideration should be given to the use of non-narcotic analgesics for patients who are depressed or suicidal.

Tramadol-related deaths have occurred in patients with previous histories of emotional disturbance or suicidal ideation, as well as histories of misuse of tranquilizers, alcohol and other CNS-active drugs.

Respiratory Depression
Tramadol + paracetamol should be administered cautiously in patients at risk for respiratory depression. Respiratory depression may result when tramadol is given in large doses with anesthetics and alcohol. Consider alternative, non-opioid analgesics for these patients.

Use with CNS Depressants
Exercise caution or reduce the dose when administering tramadol + paracetamol to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics because of increased risk of CNS and respiratory depression.

Increased Intracranial Pressure or Head Trauma
Tramadol + paracetamol should be used with caution in patients with increased intracranial pressure or head trauma. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients.

MAO Inhibitors and SSRIs
Concomitant administration of tramadol + paracetamol with MAO inhibitors and SSRIs may precipitate seizures and serotonin syndrome.

Opioid-Dependent Patients
Tramadol + paracetamol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients previously dependent on other opioids.

Acute Abdominal Conditions
Tramadol + paracetamol may complicate the clinical assessment of patients with acute abdominal conditions.

Liver Disease
The use of tramadol + paracetamol in patients with severe liver impairment is not recommended.

Renal Disease
Tramadol + paracetamol has not been studied in patients with impaired renal function.

Misuse, Abuse and Diversion
This medicine contains tramadol which can be sought by drug abusers and people with addiction disorders. The possibility of illegal or illicit use should be considered when prescribing or dispensing tramadol + paracetamol in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Misuse or abuse of tramadol + paracetamol poses a significant risk to the abuser which may result in overdose and death.

The proper management of pain should not be prevented by concerns about misuse, abuse and diversion. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Risk of Overdosage
Patients should be warned not to exceed the dose recommended by their physician. The use of tramadol in excessive doses, either alone or in combination with other CNS depressants, including alcohol, is a cause of drug-related deaths. Patients should be cautioned about the concomitant use of tramadol and alcohol because of the potentially serious CNS additive effects of these agents. Due to its added depressant effects, tramadol should be prescribed with caution in patients whose medical condition requires concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS depressant drugs.

Withdrawal
Abrupt discontinuation of tramadol + paracetamol may result in withdrawal symptoms which may include: anxiety, diarrhea, insomnia, nausea, pain, piloerection, rigors, sweating, tremors, upper respiratory symptoms, and rarely, hallucinations. Other less frequently observed symptoms include: panic attacks, paresthesias and severe anxiety. Withdrawal symptoms may be avoided by tapering the dose of the medicine at the time of discontinuation.

DRUG INTERACTIONS
TRAMADOL

CONCOMITANT DRUGS	EFFECTS
Drugs of Abuse	Additive effects may be expected when used concomitantly with other opioids (e.g., fentanyl, pethidine), or illicit drugs that cause CNS depression[e.g., gamma-hydroxybutyrate (GHB), flunitrazepam]
Carbamazepine	Decreased analgesic effect due to increased metabolism of tramadol; risk of tramadol-associated seizures. Concomitant use is not recommended
Cimetidine	No clinically significant effect on tramadol's pharmacokinetics
CYP3A4 inducers [e.g., rifampicin, St. John's Wort (*Hypericum perforatum*)]	May decrease tramadol's plasma concentration by inducing its hepatic metabolism by the isoenzyme cytochrome P450-3A4
CYP2D6 inhibitors (e.g., amitriptyline, fluoxetine, paroxetine) **and/or CYP3A4 inhibitors** (e.g., ketoconazole, erythromycin)	May reduce metabolic clearance of tramadol, thus, increasing the risk for serious adverse events including seizures and serotonin syndrome
Digoxin	Rare reports of digoxin toxicity
Quinidine	Increased plasma tramadol concentrations; decreased plasma M1 concentrations
Serotonergic Drugs: α2-adrenergic blockers (e.g., idazoxan, atipamezole); **MAO inhibitors** (e.g., selegiline, phenelzine, linezolid); **SSRIs** (e.g., fluoxetine, paroxetine); **SNRIs** (e.g., venlafaxine, duloxetine) **Triptans** (e.g., sumatriptan, naratriptan); **Lithium**	Increased risk o f serious adverse events including seizures and serotonin syndrome. Use with caution.
Warfarin	Rare alterations of warfarin effect including elevation of prothrombin time; requires monitoring.

PARACETAMOL:

CONCOMITANT DRUGS	EFFECTS
Anticonvulsants (e.g.,phenytoin, barbiturates, carbamazepine)	Increased conversion of paracetamol to hepatotoxic metabolites; increased risk of hepatotoxicity
Aspirin	No inhibition of antiplatelet effect of aspirin
Isoniazid	Possible increased risk of hepatotoxicity
Phenothiazines	Possible increased risk of severe hypothermia
Alcohol	Additive effects may be expected when used Concomitantly with alcohol (e.g., ethanol); Increased risk of paracetamol-induced hepatotoxicity
Warfarin	Rare alterations of warfarin effect including elevation of prothrombin time; requires monitoring.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS

PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tramadol + paracetamol should be used during pregnancy only if the potential benefit clearly outweighs the risks to the fetus. Chronic use during pregnancy may lead to physical dependence and neonatal withdrawal symptoms.

Tramadol crosses the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 in 40 women given tramadol during labor. Postmarketing data on tramadol HCl have reported neonatal seizures, neonatal withdrawal syndrome, fetal death, and still births. The effect of tramadol + paracetamol in the development of the child is unknown.

Lactation
The use of tramadol + paracetamol in breastfeeding mothers is not recommended because its safety in infants and newborns has not been studied.

USE IN CHILDREN
The safety and efficacy of tramadol + paracetamol in pediatric patients has not been established.

USE IN THE ELDERLY
In general, dose selection for the elderly should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function. Dose selection should also reflect the greater frequency of concomitant diseases and multiple drug therapy.

UNDESIRABLE EFFECTS
Body as a whole: asthenia, fatigue, hot flushes, chest pain, rigors, syncope, withdrawal syndrome

Gastrointestinal: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting, dysphagia, tongue edema, melena

Nervous System: dizziness, headache, tremor, ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paresthesia, stupor, vertigo
Psychiatric: anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence, amnesia, depersonalization, depression, drug abuse, bad dreams, emotional lability, hallucination, impotence, abnormal thinking, paroniria
Cardiovascular: aggravated hypertension, hypertension, hypotension, arrhythmia, palpitation, tachycardia
Respiratory: dyspnea
Hepatic: abnormal hepatic function
Metabolic: decreased weight
Hematologic: anemia
Urinary: albuminuria, micturition disorder, oliguria, urinary retention
Dermatologic: pruritus, rash, increased sweating
Special Senses: tinnitus, abnormal vision

Adverse events previously reported with tramadol hydrochloride: Vasodilation, myocardial ischemia, orthostatic hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson Syndrome/toxic epidermal necrolysis), pulmonary edema, cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure, and gastrointestinal bleeding.

Concomitant use of tramadol with other serotonergic agents such as SSRIs and MAOIs has resulted in serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures, and coma).

Reported laboratory abnormalities include elevated creatinine and liver function tests.

Adverse events previously reported with paracetamol: Allergic reactions such as skin rash or hypersensitivity secondary to paracetamol are rare. These are generally resolved by the discontinuation of the drug.

DRUG ABUSE AND DEPENDENCE

Abuse
Tramadol has μ-opioid agonist activity. Tramadol + paracetamol may be abused and may be subject to criminal diversion.

Drug addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of tramadol + paracetamol can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

Proper assessment of the patient and periodic re-evaluation of therapy are appropriate measures that help to limit the potential abuse of this product.

Dependence
Opioid abstinence or withdrawal syndrome is characterized by some or all of the following characteristics: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms include irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous therapy with tramadol + paracetamol.

OVERDOSAGE AND TREATMENT
The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both.

Tramadol overdosage and management:
Serious potential consequences of tramadol overdosage include respiratory depression, seizures, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest, and death.

Primary attention should be given in maintaining adequate ventilation along with general supportive treatment. Naloxone may reverse some, but not all symptoms caused by tramadol overdosage. Administration of naloxone also increases the risk of seizures. Hemodialysis is not expected to be helpful after tramadol overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Paracetamol overdosage and management:
Paracetamol in massive overdosage may cause hepatic toxicity in some patients. In adults and children older than 12 years, hepatic toxicity may occur after ingestion of greater than 7.5 to 10 g over a period of 8 hours or less. Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children less than 12 years old, acute overdosage with paracetamol dose of less than 150 mg/kg body weight have not been associated with hepatic toxicity. Early symptoms after a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours after paracetamol ingestion. In adults and children over 12 years, 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 N-acetylcysteine. Do not await results of assays for plasma paracetamol levels before initiating treatment with N-acetylcysteine. The following additional procedures are recommended: prompt initiation of gastric decontamination, plasma paracetamol assay (should be obtained as early as possible, but no sooner than 4 hours after ingestion) and liver function studies (should be obtained initially and repeated at 24-hour intervals).

Serious toxicity or fatalities have been rare after acute paracetamol overdose in young children, possibly because of differences in the way they metabolize paracetamol. In children, the maximum potential amount ingested can be more easily estimated. If more than 150 mg/kg or an unknown amount of paracetamol was ingested, obtain a plasma paracetamol level as soon as possible, but no sooner than 4 hours following ingestion. If an assay cannot be obtained and the estimated paracetamol ingestion exceeds 150 mg/kg, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

STORAGE CONDITION
Keep the product out of reach and sight of children.
Store at temperatures not exceeding 30°C.

AVAILABILITY
Tramadol hydrochloride + Paracetamol (**Algesia®**) 37.5/325mg tablet in blister foil of 10's box of 20's and 50's.

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

Manufactured by Amherst Laboratories, Inc.
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Trusted Quality Healthcare

Date of Revision October 2011
P30000012133
Reg. IPOPHIL