

TRADOL TABLET

COMPOSITION:

Each film-coated tablet contains: Paracetamol 325mg and Tramadol Hydrochloride 37.5mg

DESCRIPTION:

A beige color oval shaped film coated tablet

PHARMACODYNAMICS:

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is pure non selective agonists of the μ , δ , and κ opioid receptors with higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effects are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect and has no respiratory depressant effect. The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

PHARMACOKINETICS:

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.

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 %.

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.

Food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that TRADOL can be taken independently of meal times.

Distribution:

Paracetamol appears to be widely distributed throughout most body tissues except fat. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism:

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 metabolised through O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid.

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 P 450 to an active intermediate (the N-acetyl benzoquinoneimin).

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.

INDICATION:

Indicated for the management of moderate to severe pain.

RECOMMENDED DOSAGE:

Oral use

TRADOL should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with TRADOL is required as a result of nature or severity of the illness, then careful, regular monitoring should take place to assess whether continuation of the treatment is necessary.

Adults and Children Over 16 years

The maximum single dose of TRADOL is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. TRADOL can be administered without regard to food.

Children

Treatment is not recommended in this population

Elderly

In patients >75 years of age the recommended minimum interval between doses is >6 hours.

Adults and adolescents (12 years and older)

Tradol Tablet is not approved for use in patients below 12 years old.

Paediatric population

The safety and efficacy of Tradol tablet has not been studied in the paediatric population. Therefore, use of Tradol Tablet is not recommended in patients under 12 years of age.

ROUTE OF ADMINISTRATION:

Oral administration

CONTRAINDICATION:

TRADOL should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, paracetamol or any other components of this product or opioids. It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. TRADOL should not be administered to patients who are receiving monoamine oxidase inhibitors (MAOIs) or within 2 weeks of their withdrawal, patients with severe hepatic impairment and patients with epilepsy not well controlled by treatment.

- Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

WARNING AND PRECAUTIONS:

Warnings:

This preparation contains PARACETAMOL. Do not take any other paracetamol containing medicines at the same time.

Allergy alert: Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash.

These could be signs of serious condition. If these reactions occur, stop use and seek medical assistance right away.

- In adults and adolescents 12 years and older. The maximum dose of 8 tablets of TRADOL should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.

- In severe renal insufficiency (creatinine clearance <10 ml/min), TRADOL is not recommended.

- In patients with severe hepatic impairment TRADOL should not be used. The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.

In severe respiratory insufficiency, TRADOL is not recommended. 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 anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with TRADOL 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

TRADOL should be used with caution in opioid dependent patients, or 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 center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdosage may cause hepatic toxicity in some patients.

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur

Paediatric population

The safety and efficacy of Tradol tablet has not been studied in the paediatric population. Therefore, use of Tradol Tablet is not recommended in patients under 12 years of age.

Respiratory depression

Administer Tradol tablet cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even

therapeutic doses of Tradol Tradol may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism

Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Risks from Concomitant Use with Benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Tradol tablet with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Tradol tablets are used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Interactions with Other Medicaments).

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Tradol tablet with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Tradol tablet if serotonin syndrome is suspected.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-

specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience).

INTERACTION WITH OTHER MEDICAMENTS:

CYP2D6 and CYP3A4 Inhibitors

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors such as quinidine, fluoxetine, paroxetine, and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol, increasing the risk for serious adverse events including seizures and serotonin syndrome.

Serotonergic Drugs

Caution is advised when TRADOL is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, or St. John's Wort. If concomitant treatment of TRADOL with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Triptans

Based on the mechanism of action of tramadol and the potential for serotonin syndrome, caution is advised when TRADOL is coadministered with a triptan. If concomitant treatment of TRADOL with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Use With Carbamazepine

Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of TRADOL and carbamazepine is not recommended.

Use With Quinidine

Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1.

Use with Digoxin

Digoxin toxicity happens rarely.

Use with Warfarin-Like Compounds

Both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when TRADOL and warfarin-like compounds are administered concurrently.

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ -receptors, and benzodiazepines interact at GABA_A sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Tradol tablet if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

PREGNANCY AND LACTATION:

As TRADOL is a fixed combination of active ingredients containing Tramadol, it should not be ingested during lactation or pregnancy.

Tramadol and its metabolites are found in small amounts in human breast milk.

Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

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. Tradol tablet is not recommended for pregnant women.

Lactation

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.

SIDE EFFECTS:

	Side effects
Cardiovascular system	Hypertension, palpitation, tachycardia, arrhythmia, aggravated hypertension, hypotension
Central and peripheral nervous system	Dizziness, somnolence, headache, trembling, involuntary muscular contraction, paraesthesia, tinnitus, ataxia, convulsions, hypertonia, migraine, aggravated migraine, stupor, vertigo
Psychiatric	Confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders, depression, hallucinations, nightmares, amnesia, drug dependence, anorexia, depersonalization, emotional lability, importence, abnormal thinking
Vision	Blurred vision
Respiratory system	Dyspnoea
Gastro-intestinal	Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence, dysphagia, melaena, tongue edema
Liver and biliary system	Hepatic transaminases increase
Skin and appendages	Sweating, pruritus, rash
Urinary system	Albuminuria, micturition disorders (dysuria, urinary retention), oliguria
Body as whole	Shivers, hot flushes, thoracic pain, asthenia, fatigue, chest pain, rigors, syncope, withdrawal syndrome
Hearing and vestibular	Tinnitus
Metabolic and Nutritional	Weight decrease
Red blood cell disorders	Anemia

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure, and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures, and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

Other clinically significant adverse experiences previously reported with acetaminophen

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/ Toxic Epidermal Necrolysis have been reported.

Respiratory depression (rare)

Postmarketing Experience:

Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

OVERDOSAGE:

TRADOL 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 overdose may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following paracetamol overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. An overdose of TRADOL may be a potentially lethal polydrug overdose

Tramadol

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest, and death.

Deaths due to overdose have been reported with abuse and misuse of tramadol. Risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. 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.

Paracetamol

In paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects also may occur. Early symptoms following 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 post-ingestion. In the treatment of paracetamol overdosage, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity; paracetamol levels drawn less than 4 hours post ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Tramadol 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.

STORAGE:

Store below 30°C.

PRESENTATION:

Blisters of 10 tablets. Boxes of 10, 30, 60, 100, 500 and 1000 tablets.

MANUFACTURER & PRODUCT REGISTRATION HOLDER:

Noripharma Sdn. Bhd. 200701034604 (792633-A)

Lot 5030, Jalan Teratai,
5 ½ Mile off Jalan Meru,
41050 Klang, Selangor

DATE OF REVISION:

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