Paracetamol Tramadol

Nutram™

325 mg/37.5 mg Film-coated Tablet

Antipyretic/Analgesic

℞

FORMULATION:

Each film-coated tablet contains:
Paracetamol, USP .... 325 mg
Tramadol (as hydrochloride), USP .... 37.5 mg

DESCRIPTION:

Light yellow, oblong film-coated tablet.

PROPERTIES AND ACTIONS:

Tramadol is an opioid analgesic which acts on the central nervous system to block the transmission of pain signals. Tramadol mimics the action of the naturally occurring pain-relieving chemical, endorphin, found in the brain and spinal cord. Endorphins reduce pain by combining with the opioid receptors. This blocks the transmission of pain signals sent by the nerves to the brain. Tramadol also has noradrenergic and serotonergic properties that may contribute to its analgesic activity. Tramadol also works by enhancing the activity of neurotransmitters serotonin and noradrenaline in the brain and spinal cord. These are chemical compounds that act as chemical messengers between the nerve cells which also help relieve pain.

Paracetamol is a para-aminophenol derivative that has analgesic and antipyretic properties and a weak anti-inflammatory activity. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contraindicated. Such patients include asthmatics, those with a history of peptic ulcer, and children. Paracetamol relieves pain by blocking the production of prostaglandin, the chemical that causes pain, through the inhibition of the enzyme cyclooxygenase.

The combination of tramadol and paracetamol provides synergistic effect to relieve moderate to severe pain.

PHARMACOKINETICS:

After oral administration, tramadol is readily absorbed but is subject to first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use with plasma protein binding of about 20%. Tramadol is metabolized by N- and O-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite O-desmethyltramadol is pharmacologically active. Tramadol is excreted in the urine as metabolites. It may cross the placenta, and appears in small amounts in breast milk. The elimination half-life is about 6 hours.

After oral administration, paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 mins after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolized mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (N-acetyl-p-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

INDICATIONS:

Management of moderate to severe pain.

DOSAGE AND ADMINISTRATION:

1-2 tablets every 4-6 hours or as needed for pain relief up to a maximum of 8 tablets a day.

Children: Not recommended.

Elderly patients: The usual doses maybe used, but the interval between doses should not be less than 6 hours.

Renal insufficiency: Not recommended for patients with severe renal insufficiency or those with creatinine clearance less than 10 ml/min.

In case of moderate renal insufficiency or those with creatinine clearance of less than 30 ml/min, the dosage interval should be increased to 12 hours.

Hepatic Insufficiency: Not recommended for patients with severe hepatic impairment.

CONTRAINDICATIONS/PRECAUTIONS/WARNINGS:

Paracetamol + Tramadol (Nutram™) should not be given to patients who have previously demonstrated hypersensitivity reactions to tramadol, paracetamol and any other components of the drug.

Other contraindications include: patients who are addicted to drugs affecting the CNS such as alcohol, hypnotics, centrally-acting analgesics and anti-psychotic drugs; patients with epilepsy not controlled by treatment; patients at risk of mental fog caused by head injury or brain lesion; patients with acute respiratory depression, and those with a history of aspirin-sensitive asthma.

Paracetamol + Tramadol may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

Opioid analgesics should be stopped gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms. If opioids like tramadol are discontinued abruptly, symptoms of withdrawal reactions may occur which include: yawning, mydriasis, lachrymation, rhinorrhea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhea, dehydration, leukocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Panic attacks, hallucinations, paresthesia, and unusual CNS symptoms have rarely been reported.

Tramadol should be used with caution in patients with hepatic or renal impairment, and should not be used in patients with severe renal impairment. Tramadol should be used with care in patients with history of epilepsy or those who are susceptible to seizures. It should not be given to patients who are suicidal or prone to addiction. It should be used with caution in those who use alcohol in excess or suffer from emotional disturbances or depression.

As tramadol is a type of opioid analgesic, precautions and contraindications to opioid analgesics should also be considered. Opioid analgesics are generally contraindicated in acute respiratory depression and obstructive airway disease. They are also contraindicated or should be used with great caution in acute alcoholism, convulsive disorders, head injuries, and conditions in which intracranial pressure is raised. They should not be given to comatose patients. They have an inhibitory effect on gastrointestinal motility and should be avoided in patients at risk of paralytic ileus.

Opioid analgesics should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma or decreased respiratory reserve, renal or hepatic impairment, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, or myasthenia gravis. Dosage should be reduced in elderly or debilitated patients.

Opioid analgesics may occasionally cause adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g., severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite and weight loss.

Ageing can affect the pharmacokinetics and pharmacodynamics of opioids although the effects of these changes on opioid analgesia in the elderly remain unclear. Recommendations include careful review of indication for opioid use both initially and at regular intervals thereafter, starting opioids cautiously at lower doses and with longer dosing intervals, and regular consideration given to dose reduction and drug substitution or discontinuation. If possible, further drugs should not be prescribed to manage the adverse effects of opioids.

Opioid analgesics should be given with great caution to infants, especially neonates. Use of opioid analgesics during labor may cause respiratory depression in the neonate. Babies born to opioid-dependent mothers may suffer withdrawal symptoms. Children under 6 months of age may be more sensitive to opioids.

The pharmacokinetics of opioids may be altered in patients with hepatic dysfunction. It has been recommended that oral immediate-release or parenteral, short-acting opioids were preferable to long-acting preparations such as transdermal or modified-release formulations.

It is usually recommended that opioids should either be avoided in patients with biliary disorders.

Paracetamol should also be given with care to patients with alcohol dependence, chronic malnutrition, dehydration and those with impaired kidney and liver function. Large doses of paracetamol should be avoided in patients with liver impairment.

PREGNANCY AND LACTATION:

Safe use of tramadol in pregnancy and lactation has not been established.

DRUG INTERACTIONS:

Concomitant use of tramadol and carbamazepine is not recommended. Patients taking carbamazepine may have a significantly reduced analgesic effect or shorter duration of action of tramadol, because carbamazepine increases tramadol metabolism and reduces serum concentration. The risk of seizure is increased if tramadol is used with other drugs that have the potential to lower the seizure threshold.

Tramadol inhibits reuptake of noradrenaline and serotonin and enhances serotonin release and there is the possibility that it may interact with other drugs that enhance monoaminergic neurotransmission including lithium, tricyclic antidepressants, triptans, and SSRIs.

Tramadol may increase the risk of seizures in patients taking SSRIs, TCA, other tricyclic drugs (promethazine), and other opioids, MAO inhibitors, neuroleptics or other medications that lower the seizure threshold. Tramadol should not be given to patients receiving MAOI's or within 14 days of their discontinuation. The post-operative analgesic efficacy of tramadol may be reduced by the pre-operative use of ondansetron.

Metabolism of tramadol is mediated by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Use with specific inhibitors of these enzymes, such as quinidine, may increase concentrations of tramadol and lower concentrations of its active metabolite. The clinical consequences of this effect are unclear although the risk of seizures or serotonin syndrome may be increased.

Use of paracetamol + tramadol while taking warfarin may result in enhanced anticoagulant activity.

There is an increased risk of paracetamol toxicity in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. Metoclopramide may increase the absorption of paracetamol. Excretion of paracetamol may be affected and its plasma concentrations may be altered when given with probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. Although urinary excretion of the sulfate and glucoronide conjugates of paracetamol are reduced, that of paracetamol is unchanged. Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole.

Paracetamol has also been found to enhance the antiviral effect of interferon alfa in healthy subjects.

Other drugs that may interact with paracetamol includes rifampicin, isoniazid, chloramphenicol, warfarin, carbamazepine, phenobarbital, phenytoin, and primidone.

ADVERSE DRUG REACTIONS:

Skin: pruritus, rashes, urticaria

Central Nervous System: dizziness, headache, constriction or dilation of the pupils, numbness of extremities, dysphoria, tremors, convulsion, ataxia, confusion, hallucinations, insomnia, nervousness, paresthesia, involuntary muscle contraction, and vertigo.

Cardiovascular System: occasionally hypertension, hypotension, palpitation, tachycardia, and arrhythmia.

Gastrointestinal tract: abdominal pain, nausea, constipation, diarrhea, dyspepsia, flatulence, dry mouth, and vomiting.

Respiratory system: occasionally: dyspnea. frequency unknown: hiccups

Others: hepatic dysfunction, weight loss, tinnitus, abnormal vision, orthostatic hypotension, cognitive dysfunction, and hepatitis.

There have been death related-reports associated with the use of tramadol among patients with history of emotional disturbances, suicidal ideation or misuse of CNS depressants such as alcohol and anxiolytics.

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally.

Other reported adverse effects of paracetamol include hearing loss, nephropathy, pyroglutamic aciduria, and metabolic acidosis.

OVERDOSE AND TREATMENT:

Common signs and symptoms of tramadol toxicity include lethargy, nausea, vomiting, tachycardia, agitation, seizures, and respiratory depression.

In cases of overdosage, the specific antagonist naloxone is used for rapid reversal of the severe respiratory depression and coma produced by excessive doses of opioid analgesics. Intensive supportive therapy may be required to correct respiratory failure and shock.

Activated charcoal may be given orally in conscious patients if a substantial overdose has been ingested within 1 hour provided that the airway can be protected.

Since naloxone has a shorter duration of action than many opioids, patients who have already responded should be kept under close observation for signs of relapse and repeated administration is given according to the respiratory rate and depth of coma. Alternatively, in situations where repeated administration is required, such as where a longer acting opioid is known or suspected to be the cause of symptoms, a continuous intravenous infusion of naloxone is given and adjusted depending on the response of the patient. All patients should be observed for at least 6 hours after the last dose of naloxone.
The use of opioid antagonist such as naloxone in persons physically dependent on opioids may induce withdrawal symptoms.

Toxic doses of paracetamol may cause severe hepatocellular necrosis and less often, renal tubular necrosis. Paracetamol-induced hepatotoxicity is a major cause of acute liver failure. Hepatotoxicity may occur after ingestion of more than 150mg/kg or rarely, as little as 75 mg/kg of paracetamol within a 24-hour period. Signs and symptoms of paracetamol overdosage may include nausea, vomiting, sweating, lethargy and abdominal pain.

Appropriate and prompt expert consultation is recommended since overdose of tramadol plus paracetamol may be potentially lethal. Primary attention should be given to maintain adequate ventilation along with general supportive measures. Efforts should be taken to reduce drug absorption. Adequate fluid management should be employed to counteract hypotension. Vasopressors and other supportive measures are administered as indicated.

Activated charcoal may be used in the treatment of oral overdosage to reduce gastrointestinal absorption. There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.

Acetylcysteine is the antidote of choice for paracetamol toxicity but the route of administration varies and the best protocol has yet to be determined. It is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter.

Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamol overdosage. However, it is not as effective if treatment is delayed. It has also been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Liver transplantation may be considered as a last recourse in some patients.

After maternal overdosage during pregnancy, fetal metabolism of paracetamol that crosses the placenta can produce sufficient hepatotoxic metabolites to cause fetal hepatotoxicity. Limited data from case reports and a case series suggest that early treatment with oral or intravenous acetylcysteine can be safe and effective in such cases. Pre-pregnancy body-weight should be used to calculate the toxic paracetamol dose and actual pregnant body-weight to calculate the antidote dose.

CAUTION:

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

AVAILABILITY:

Alu/PVC blister pack of 10's, box of 30 film-coated tablets.

DR-XY40688

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

For suspected adverse drug reaction: report to the FDA www.fda.gov.ph
Seek advice from a healthcare professional at the first sign of any adverse drug reaction.

SVMore

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5th Flr., S.V. More Group Corporate Center
#16 Scout Tuazon cor. Roces Ave., Laging Handa, Quezon City, Metro Manila, Philippines

Imported by: **DAEWOONG PHARMA PHILS., INC.**
Unit 1701, 17th Floor, One World Place Condominium,
32nd Street, Bonifacio Global City Fort Bonifacio, Taguig, Metro Manila

Manufactured by: **DAEWOONG PHARMACEUTICAL CO. LTD.**
35-14, Jeyakgongdan 4-gil, Hyangnam-eup, Hwaseong-Si, Gyeonggi-Do, Korea

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