Paracetamol
Tramadol HCl

Nutram
325 mg/37.5 mg Film-coated Tablet

Analgesic

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

PROPERTIES AND ACTIONS:
The combination of Tramadol HCl and Paracetamol provides double analgesic benefits for moderate to severe pain. 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, endorphins, found in the brain and spinal cord. Endorphin reduces pain by binding to 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 nerve cells which also help relieve pain.

Paracetamol is a para-aminophenol derivative which has analgesic and antipyretic properties, and a weak anti-inflammatory activity. 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:
Tramadol is readily absorbed following oral administration but is subject to first-pass metabolism. 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 mainly in the urine. It crosses the placenta, and appears in small amounts in breast milk. The elimination half-life following oral administration is about 6 hours.

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.

INDICATIONS:
Management of moderate to severe pain.

CONTRAINDICATIONS:
Paracetamol + Tramadol HCl (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 severe respiratory depression, and those with a history of aspirin-

sensitive asthma; patients with hematological abnormality and patients with peptic ulcer disease.
Paracetamol + Tramadol HCl should be avoided if renal impairment is severe.

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.

ADVERSE EFFECTS:
Skin: pruritus, rashes, urticaria

Central Nervous System (CNS): dizziness, headache, tremors, convulsion, ataxia, confusion, hallucinations, insomnia, nervousness, paresthesia, involuntary muscle contraction, vertigo.

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

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

Respiratory system: occasionally dyspnea.

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

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

DRUG INTERACTIONS:
Tramadol may increase the risk of seizures in patients taking Selective Serotonin Reuptake Inhibitors (SSRI), Tricyclic Antidepressants (TCA), other tricyclic drugs (promethazine), and other opioids, Monoamine Oxidase Inhibitors (MAOI), neuroleptics, or other medications that lower the seizure threshold. Tramadol should not be given to patients receiving MAOIs or within 14 days of their discontinuation.

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.

Other drugs such as erythromycin and ketoconazole, might inhibit the metabolism of tramadol.

Metabolism of tramadol is mediated by the cytochrome P450 isoenzyme CYP2D6. Use with specific inhibitors of this enzyme, such as quinidine, may increase concentrations of tramadol and lower concentrations of its active metabolite, but the clinical consequences of this effect are unclear.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations are altered when given with probenecid. Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

WARNINGS AND SPECIAL PRECAUTIONS:
Tramadol should be used with caution when administered to patients taking CNS depressants such as: alcohols, opioids, narcotics, sedatives, phenothiazines, hypnotics, antihistamines, neuroleptics, centrally acting antihypertensive drugs. These drugs may increase the risk of CNS and respiratory depression.

Convulsion have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold especially SSRIs, TCAs, antipsychotics and other opioids.

If tramadol is discontinued abruptly, symptoms of withdrawal reactions may occur which include anxiety, sweating, insomnia, pain, nausea, tremors, diarrhea, respiratory tract infection, keratosis pilaris, agitation, nervousness, hyperkinesias, and gastrointestinal symptoms. 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, history of epilepsy or those susceptible to seizures.

Paracetamol should be given with care to patients with impaired kidney and liver function. It should also be given with care to patients with alcohol dependence.

Overdosage of paracetamol may increase hepatic toxicity to patients with chronic alcoholism.

Pregnancy and lactation:
Paracetamol is generally considered to be the analgesic of choice in pregnant patients. Safe use of tramadol in pregnancy and lactation has not been established.

Effects on ability to drive and operate machines:
Tramadol may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

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.

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

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