PRESCRIBING INFORMATION: For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

GABAPIN NT

(Gabapentin & Nortriptyline Hydrochloride Tablets)

COMPOSITION

GABAPIN NT
Each film coated tablet contains:

Gabapentin USP	400 mg
Nortriptyline Hydrochloride IP equivalent to Nortriptyline	10 mg
Colour: Titanium Dioxide IP	
Excipients:	Q.S.

GABAPIN NT 100
Each film coated tablet contains:

Gabapentin USP	100 mg
Nortriptyline Hydrochloride IP equivalent to Nortriptyline	10 mg
Colour: Titanium Dioxide IP	
Excipients:	Q.S.

DESCRIPTION

GABAPIN NT is a fixed-dose combination product containing gabapentin and nortriptyline. It is intended for oral use in neuropathic pain.

Gabapentin is basically an anticonvulsant. It also alleviates neuropathic pain. Chemically gabapentin is described as 1-(Aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24.

Nortriptyline hydrochloride is a tricyclic antidepressant. It is a metabolite of amitriptyline which is also used as an antidepressant. The chemical name of nortriptyline hydrochloride is 1-Propanamine, 3-(10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-N-methyl-, hydrochloride. Its molecular formula is $C_{19}H_{21}N$•HCL and molecular weight 299.84.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Gabapentin

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. It acts as a neuromodulator by selectively binding to $alpha_2$-delta subunit protein of the neuronal calcium channel in various regions of the brain and the superficial dorsal horn of the spinal cord. The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice. Gabapentin also decreases pain-related responses after peripheral inflammation.

Nortriptyline

Nortriptyline inhibits the neuronal reuptake of the norepinephrine (NE), as well as serotonin (5-HT). It is relatively more selective inhibitor of NE reuptake. Nortriptyline is thought to promote accumulation of NE and 5-HT in the descending inhibitory pathways from the brain to the spinal cord that modulate pain impulse transmission. NE and 5-HT being the principal neurotransmitters in these pathways, activation of these pathways by nortriptyline results in enhanced negative modulation of pain impulse transmission. This action may account for decreased perception of neuropathic pain.

PHARMACOKINETICS

Gabapentin

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Food has only a slight effect on the rate and extent of absorption of gabapentin. Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (Mean ± SD). Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing.

Nortriptyline

Most tricyclic antidepressants are incompletely absorbed and undergo significant first-pass metabolism. The absolute oral bioavailability of nortriptyline is 32-79%. Nortriptyline is 92% bound to plasma proteins. It has relatively high lipid solubility; volumes of distribution tend to be very large (about 1300L/kg). Nortriptyline has mainly hepatic metabolism and is metabolized to form active 10-hydroxy derivatives. The oral clearance of nortriptyline is 30 L/hr; very small amount of the drug (about 2%) is excreted via urine. The mean terminal half-life of nortriptyline is 21-57 hours. Nortriptyline follows linear pharmacokinetics and therapeutic plasma concentration range is approximately 50-150 ng/ml.

INDICATIONS

GABAPIN NT is indicated for the treatment of pain associated with peripheral neuropathic conditions in adults.

CONTRAINDICATIONS

GABAPIN NT is contraindicated in the following conditions:

1) Hypersensitivity to gabapentin or nortriptyline, other tricyclic antidepressants, or to any ingredient in the formulation
2) Pregnancy and lactation
3) Acute recovery period after myocardial infarction
4) Concomitant use with monoamine oxidase inhibitors

DOSAGE AND ADMINISTRATION

GABAPIN NT is given orally with or without food. If GABAPIN NT dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber).

In adults with painful neuropathic conditions such as post-herpetic neuralgia, GABAPIN NT therapy should be initiated as a single tablet taken on day 1, one tablet to be taken twice daily day 2, one tablet thrice a day (t.i.d.) on day 3 and thereafter the dose can be titrated up as needed for pain relief by successively adding one tablet to existing t.i.d. regimen to reach the maximum recommended dose of 2400 mg gabapentin or 60 mg nortriptyline per day. Attempt should be made to titrate the dosage to a maintenance level that is well tolerated as well as effective. Periodic reassessment of the patient for his need to take GABAPIN NT should be made.

Use in Special Population

Pediatric Use

Use of GABAPIN NT in pediatric patients is not recommended.

Geriatric Use

GABAPIN NT should be used cautiously in elderly subjects.

Gabapentin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

The safety and effectiveness of nortriptyline in the geriatric population have not been established fully.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

Use in Pregnancy and Lactation

Use of GABAPIN NT is not recommended.

Gabapentin

Pregnancy Category C.

Nortriptyline

Pregnancy Category D.

Dosage in Renal Impairment

In adult and elderly patients with renal impairment the recommended dosages of GABAPIN NT are as follows:

Renal Function [Creatinine Clearance] (ml/min)	GABAPIN NT Tablet Dosage (No. of tablets per day)	GABAPIN NT 100 Tablet Dosage (No. of tablets per day)
≥60	1-4	1-6
≥30-59	1-3	1-6
≥15-29	1-2	1-6
15	Not recommended	1-3

Dosage in Hepatic Impairment

Dosage adjustment of GABAPIN NT is not needed in mild to moderate hepatic impairment. It is not recommended for use in severe hepatic impairment.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk

Antiepileptic drugs, including gabapentin and antidepressant drugs, including nortriptyline can increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Families and caregivers of patients being treated with antidepressants or antiepileptics for any indications should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies with gabapentin an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female rats.

Sudden and Unexplained Death in Patients with Epilepsy

In post-marketing study sudden and unexplained death in patients with epilepsy had been reported with use of gabapentin.

Additional Precautions

Gabapentin

1) Patients should be advised that gabapetntin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a vehicle nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

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Nortriptyline

1) Patients with bipolar disorder: It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder.
2) Patients with a history of seizures should be followed closely when nortriptyline is administered, as this drug is known to lower the convulsive threshold.
3) Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin

A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose of gabapentin. Gabapentin did not demonstrate mutagenic or genotoxic potential *in vitro* and *in vivo* assays. No adverse effects on fertility or reproduction were observed in rats.

Nortriptyline

Studies are not described.

DRUG INTERACTIONS

Gabapentin

(1) Coadministration with naproxen, hydrocodon, morphine can leads to increased bioavailability of gabapentin.
(2) Cimetidine and probenecid coadministration can alter the renal excretion of gabapentin.
(3) Antacid like aluminum hydroxide and magnesium hydroxide can reduce the bioavailability of gabapentin.
(4) The peak plasma concentration of norethindrone can increase when orally coadministered with gabapentin.
(5) Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs such as phenytoin, carbamazepine, valproic acid and phenobarbitone.

Nortriptyline

(1) Close supervision and careful adjustment of the dosage are required when nortriptyline hydrochloride is used with other anticholinergic drugs and sympathomimetic drugs.
(2) Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant.
(3) The patient should be informed that the response to alcohol may be exaggerated.
(4) Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.
(5) A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).
(6) Concomitant use of nortriptyline with drugs that can inhibit cytochrome P450 2D6 such as selective serotonin reuptake inhibitors (SSRIs), viz., fluoxetine, sertraline, and paroxetine may require lower doses than usually prescribed.

ADVERSE EFFECTS

Adverse effects to GABAPIN NT pertain to those associated with the use of its two individual components.

Gabapentin

The most commonly reported adverse events associated with the use of gabapentin in adults are dizziness, somnolence, and peripheral edema.

Other important side effects, system-wise, are mentioned below:

Body as a Whole: asthenia, malaise, face edema, allergy, generalized edema
Cardiovascular System: hypertension, hypotension, palpitation, tachycardia, murmur
Digestive System: anorexia, flatulence, gingivitis, glossitis, stomatitis
Endocrine System: hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance
Hematologic and Lymphatic System: purpura; thrombocytopenia
Musculoskeletal System: arthralgia, tendinitis, arthritis, joint stiffness, joint swelling
Nervous System: vertigo, hyperkinesia, paresthesia, ataxia, tremors; dystonia, decreased or absent reflexes, increased reflexes, anxiety, hostility, syncope, dreaming abnormal, aphasia, hypoesthesia, intracranial hemorrhage, hypotonia, dysesthesia
Psychiatric: exacerbation of psychoses, euphoria, agitation, paranoia
Respiratory System: pneumonia, epistaxis, dyspnea, apnea
Dermatological: alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea
Urogenital System: hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal
Special Senses: abnormal vision, hearing loss, earache, tinnitus, unusual taste

Nortriptyline

The most commonly reported side effects with nortriptyline are hypotension, sedation, dry mouth, seizures, weight gain, gynecomastia in the male, and breast enlargement and galactorrhea in the female.

Other important side effects, system-wise, are mentioned below:

Cardiovascular System: hypertension, hypotension, palpitation, tachycardia, murmur
Nervous System: numbness, tingling, incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms, alteration in EEG patterns, tinnitus.
Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis, euphoria
Allergic: skin rash, petechiae, urticaria, itching, photosensitization, edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs
Anticholinergic: dry mouth, blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus, urinary retention, delayed micturition, dilation of the urinary tract
Digestive System: nausea and vomiting, anorexia, diarrhea, abdominal cramps, black tongue
Endocrine System: gynecomastia in the male, breast enlargement and galactorrhea in the female
Hematological and lymphatic system: bone marrow depression, agranulocytosis, eosinophilia
Other: jaundice (simulating obstructive), altered liver function, weight gain or loss
Withdrawal Symptoms: though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSE

Symptoms

Gabapentin

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed.

Nortriptyline

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, shock, congestive heart failure, pulmonary edema, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. Other signs of overdose may include: confusion, restlessness, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the acute symptoms listed under ADVERSE EFFECTS.

Management

Gabapentin

There is no specific antidote. Patients recovered with supportive care. Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

Nortriptyline

There is no specific antidote. There have been reports of patients recovering from nortriptyline overdoses of up to 525 mg with no associated fatalities.

General

The main treatment of toxicity is symptomatic and includes specifically the basic management of airway and respiration. Gastric lavage with activated charcoal should be done. Vital sign monitoring along with general symptomatic and supportive care is required.

Supportive Therapy

The electrocardiogram, pulse, blood pressure, neurobehavioral status of the patient and his intake and output balance must be monitored. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines. Psychiatric referral may be appropriate for nortriptyline overdosage after emergency management.

STORAGE

Store below 30°C, protected from light & moisture.

PRESENTATION

GABAPIN NT & GABAPIN NT 100 is available in a pack of 15's Tablets.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

Bhagey Khola, Rangpo, East Sikkim-737 132, INDIA

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