Gabaring™ NT

Gabapentin 400mg + Nortriptyline 10mg Tablets

The RING Champion

1. **Generic Name**

Gabapentin

Nortriptyline

2. **Qualitative and Quantitative composition**

Gabapentin – 400mg

Nortriptyline- 10mg

3. **Dosage form and strength**

Oral tablets containing Gabapentin 400mg and Nortriptyline 10mg

4. **Clinical particulars**

4.1 Therapeutic indication

Gabaring NT is indicated in treatment of:

- Severe neuropathic Pain
- Management of refractory NP
- Post herpetic Neuralgia

Gabaring NT is used to treat long-lasting (chronic) pain caused by nerve damage due to diabetes, shingles or spinal cord injury.

It reduces pain and its associated symptoms such as mood changes, sleep problems, and tiredness.

4.2 Posology and method of administration

As directed by physician.

4.3 Contraindication

- Hypersensitivity to the active substance.
- Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated.

Simultaneous administration of Gabaring NT and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

- Treatment with Gabaring NT may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of Gabaring NT.
- Recent myocardial infarction, any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency

4.4 Special warnings and precautions for use

- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking antiepileptic drugs including gabapentin

- Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue Gabaring NT and seek immediate medical care.

- Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

- Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations.

Concomitant administration of nortriptyline and opioid products (e.g., Buprenorphine) may result in serotonin syndrome, a potentially life-threatening condition. Symptoms of serotonin

syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

- Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

- QT interval prolongation

Cases of QT interval prolongation and arrhythmia have been reported. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrhythmic risk.

4.5 Drug interactions

- Contraindicated combinations

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) - risk of "serotonin syndrome"

- Combinations that are not recommended

<u>Sympathomimetic agents</u>

Nortriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine

<u>Adrenergic neurone blockers/antihypertensives</u>

Nortriptyline may decrease the antihypertensive effect of guanethidine, debrisoquine, bethanidine, methyldopa and possibly clonidine. Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients. It would be is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

<u>Anticholinergic agents</u>

Tricyclic antidepressants may potentiate the effects of these medicinal products on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

Drugs which prolong the QT-interval, including antiarrhytmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants.

Use caution when using nortriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

Caution is also advised for co-administration of nortriptyline and diuretics inducing hypokalaemia (e.g. furosemide).

Thioridazine: Co-administration of nortriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects

Tramadol: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as nortriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

Opioids: Nortriptyline should be used cautiously when co-administered with opioids (e.g. Buprenorphine), as the risk of serotonin syndrome, a potentially life-threatening condition, is increased. There are spontaneous and literature case reports of respiratory depression and/or sedation and death associated with gabapentin when co-administered with CNS depressants, including opioids.

Antifungals such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

- Combinations requiring precautions for use

Co-administration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

CNS depressants: Nortriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.

CYP2D6 inhibitors: The CYP2D6 isozyme can be inhibited by a variety of medicinal products, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-

administered with another medicinal product known to be an inhibitor of CYP2D6. Dose adjustment of nortriptyline may be necessary.

Other Cytochrome P450 inhibitors: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity.

Cytochrome P450 inducers: Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (Hypericum perforatum) may increase the metabolism of tricyclic antidepressants and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

Nortriptyline plasma concentration can be increased by valproic acid. Clinical monitoring is therefore recommended.

4.6 Use in special population

- Pediatric: Safety and efficacy have not been established.
- Geriatric: No systematic studies in patients 65 years or older have been conducted.
- Liver impairment: In case of reduced liver function careful dosing and, if possible, a serum level determination is advisable.
- Renal failure: Dosage adjustment is recommended in patients with compromised renal function.
- Pregnancy and lactation: There are no or limited amount of data from the use of Gabaring NT in pregnant women.
  Both drugs are excreted in human milk. Gabaring NT should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Gabaring NT is known.

4.8 Undesirable effects

- Gabapentin

Thrombocytopenia, Anaemia, Leukopenia, Neutropenia, cardiac arrest, palpitations, cardio-respiratory arrest, myocardial infraction, tachycardia, cardiac disorder, vertigo, tinnitus, hypoacusis, deafness, thyroid disorder, vision blurred, visual impairment, diplopia, nausea, vomiting, diarrhoea, constipation, dry mouth, dyspepsia, pain, fatigue, feeling abnormal, asthenia, peripheral swelling, hepatitis, weight increased, weight decreased, blood pressure

increased, blood glucose increased, blood cholesterol increased, decreased appetite, diabetes mellitus, fluid retention, pain in extremity, arthralgia, muscle spasms, back pain, myalgia, dizziness, somnolence, headache, tremor, seizures, memory impairment, hypoaesthesia, amnesia, neuropathy peripheral, suicidal, insomnia, depression, confusional state, anxiety, hallucinations, agitation, dyspnoea, respiratory arrest, cough, asthma, rash, pruritus, urticaria, hyperhidrosis, alopecia, hypertension, hypotension, hot flush, flushing,

- Nortriptyline

Thrombocytopenia, tachycardia, palpitations, tinnitus, visual impairment, dry mouth, constipation, nausea, dyspepsia, jaundice, weight increased, arthralgia, dizziness, somnolence, headache, tremor, seizure, insomnia, anxiety, depression, suicide attempt, delirium, dyspnoea, rash, hyperhidrosis, hypotension.

4.9 Overdose

There is limited experience of overdose with Gabaring NT Tablets. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

Gabapentin

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α2δ.

Nortriptyline

Nortriptyline is an antidepressant that falls under the pharmacological category of tricyclics (secondary amine), more commonly known as TCAs.

The consensus is that nortriptyline inhibits the reuptake of serotonin and norepinephrine by the presynaptic neuronal membrane, thereby increasing the concentration of those neurotransmitters in the synapse. Additionally, nortriptyline inhibits the activity of histamine, 5-hydroxytryptamine, and acetylcholine. Nortriptyline increases the pressor effect of norepinephrine but hinders the pressor response of phenethylamine. However, research has found additional receptor effects, including desensitization of adenylyl cyclase, down-regulation of beta-adrenergic receptors, and downregulation of serotonin receptors.

5.2 Pharmacodynamic properties

Gabapentin

Gabapentin is an anti-convulsant medication that inhibits the release of excitatory neurotransmitters, allowing for its use against pathologic neurotransmission such as that seen in neuropathic pain and seizure disorders.16,19 It has a wide therapeutic index, with doses in excess of 8000 mg/kg failing to cause a fatal reaction in rats.

Nortriptyline

Nortriptyline exerts antidepressant effects likely by inhibiting the reuptake of serotonin and norepinephrine at neuronal cell membranes. It also exerts antimuscarinic effects through its actions on the acetylcholine receptor.

5.3 Pharmacokinetic properties

Gabapentin

Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Biotransformation

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.

Nortriptyline

Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites). N-oxidation and conjugation with glucuronic acid. Nortriptyline is widely distributed throughout the body and is extensively bound to plasma and tissue protein. Plasma concentrations of Nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

6. Nonclinical properties

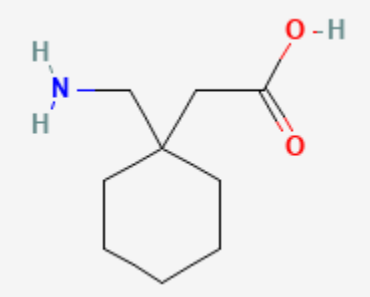
6.1 Animal Toxicology or Pharmacology

Not required.

7. Description

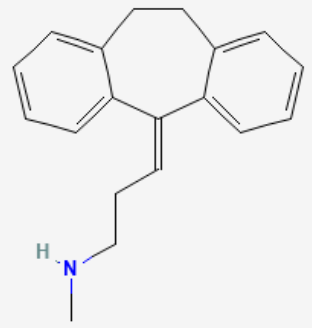
Gabapentin

Gabapentin is a synthetic analogue of the neurotransmitter gamma-aminobutyric acid with anticonvulsant activity. The chemical name is 2-[1-(aminomethyl)cyclohexyl]acetic acid. Its empirical formula is $C_9H_{17}NO_2$ and molecular weight is 171.24.



Nortriptyline

Nortriptyline is a tricyclic antidepressant agent used for short-term treatment of various forms of depression. Its chemical name is N-methyl-3-(2-tricyclo[9.4.0.0]pentadeca-1(15),3,5,7,11,13-hexaenylidene)propan-1-amine. Its empirical formula is $C_{19}H_{21}N$ and mol wt is 263.4



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Gabaring NT is available in pack of 10 tablets.

8.4 Storage and handling instructions

Store in a cool and dry place away from sunlight.

9. Patient Counselling Information

9.1 Adverse reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.8

9.3 Dosage

Refer part 4.5

9.4 Storage

Refer part 8.4

9.5 Risk factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. PURE AND CURE HEALTHCARE PVT LTD

11. Manufacturing license number : F.No. 17p/1/222/2013/1508

12. Date of revision: January 2022