For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

GABATOR NT

1. Generic Name

Gabapentin & Nortriptyline Hydrochloride Tablets

2. Qualitative and quantitative composition

GABATOR NT 100

Each film coated tablet contains:

Gabapentin I.P. …….....100 mg

Nortriptyline Hydrochloride I.P.

Eq. to Nortriptyline ….....….10 mg

Colour: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Lactose, Starch, PVP-K-30, Colloidal Silicone Dioxide, Magnesiun Stearate, Croscarmellose Sodium, Crospovidone, Seal Coat TR, Talcum, Super Coat Film, Titanium Dioxide, Isopropyl Alcohol.

GABATOR NT 200

Each film coated tablet contains:

Gabapentin I.P. …….....200 mg

Nortriptyline Hydrochloride I.P.

Eq. to Nortriptyline ….....….10 mg

Colour: Titanium Dioxide I.P.

The excipients used are Starch, Microcrystalline Cellulose, Hydroxy Propyl Celloulose, Colloidal Silicone Dioxide, Magnesiun Stearate, Super Coat, Talcum, Titanium Dioxide, Isopropyl Alcohol, Methylene Chloride.

GABATOR NT 300

Each film coated tablet contains:

Gabapentin I.P. …….....300 mg

Nortriptyline Hydrochloride I.P.

Eq. to Nortriptyline ….....….10 mg

Colour: Titanium Dioxide I.P.

The excipients used are Sodium Starch Glycolate, Pregelatinized Starch, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Di-Sodium Ededate, Microcrystalline Cellulose, Colloidal Silicone Dioxide, Talcum, Magnesium Stearate, Instamoist Shiled, Methylene Chloride.

GABATOR NT 400

Each film coated tablet contains:

Gabapentin I.P. …….....400 mg

Nortriptyline Hydrochloride I.P.

equivalent to Nortriptyline …….10 mg

Colour: Titanium Dioxide I.P.

The excipients used are Starch, Plasdone S-630, Polyvinyl Pyrrolidone, Pregelatinized Starch, Croscarmellose sodium, Colloidal Sillicon Dioxide, Talc, Magnesium Stearate, Protectab HP 1, Titanium Dioxide, Isopropyl alcohol and Methylene chloride.

3. Dosage form and strength

Dosage form: film coated tablet

Strength: 100, 200, 300 and 400 mg

4. Clinical particulars

4.1 Therapeutic indication

GABATOR NT is indicated for neuropathic pain in adults.

4.2 Posology and method of administration

Posology

Gabapentin:

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1		
DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300mg once a day	300mg two times a day	300mg three times a day

Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Peripheral neuropathic pain

Adults

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300mg/day increments every 2-3 days up to a maximum dose of 3600mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800mg/day is one week, to reach 2400mg/day is a total of 2 weeks, and to reach 3600mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Elderly (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age. Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

Renal impairment

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2	
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION	
Creatinine Clearance (ml/min)	Total Daily Dose[a] (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b] -600
<15[c]	150[b] -300

[a] Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79ml/min).

[b] The 150mg daily dose to be administered as 300mg every other day.

[c] For patients with creatinine clearance <15ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15ml/min receive).

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg, then 200 to 300mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300mg dose following each 4-hour haemodialysis treatment is recommended.

Nortriptyline

*Adults***:** The usual adult dose is 25mg three or four times daily. Dosage should begin at a low level and be increased as required. Alternatively, the total daily dose may be given once a day. When doses above 100mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150ng/ml. Doses above 150mg per day are not recommended.

Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalised patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

If a patient develops minor side-effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Elderly: 30 to 50mg/day in divided doses.

Adolescent patients: 30 to 50mg/day in divided doses.

Plasma levels: Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150ng/ml. Higher concentrations may be associated with more adverse experiences. Plasma concentrations are difficult to measure, and physicians should consult the laboratory professional staff.

Many antidepressants (tricyclic antidepressants, including nortriptyline, selective serotonin re-uptake inhibitors and others) are metabolised by the hepatic cytochrome P450 isoenzyme P450IID6. Three to ten per cent of the population have reduced isoenzyme activity ('poor metabolisers') and may have higher than expected plasma concentrations at usual doses. The percentage of 'poor metabolisers' in a population is also affected by its ethnic origin.

Older patients have been reported to have higher plasma concentrations of the active nortriptyline metabolite 10-hydroxynortriptyline. In one case, this was associated with apparent cardiotoxicity, despite the fact that nortriptyline concentrations were within the 'therapeutic range'. Clinical findings should predominate over plasma concentrations as primary determinants of dosage changes.

Paediatric population

Nortriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established.

Method of administration

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
- Severe liver disease.
- Mania.
- Nortriptyline is contra-indicated for the nursing mother and for children under the age of six years.

4.4 Special warnings and precautions for use

Gabapentin

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.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

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 gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin in the post-marketing experience.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Discontinuation of gabapentin treatment should be considered in case of suicidal ideation and behaviour.

Acute pancreatitis

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered.

Seizures

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

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. The dose of gabapentin or concomitant treatment with CNS depressants including opioids should be reduced appropriately.

Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a reported population-based, observational, nested case-control study of opioid users, co prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88, p<0.001]).

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.

Elderly (over 65 years of age)

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one reported double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

Paediatric population

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Abuse and Dependence

Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.

Laboratory tests

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Nortriptyline

Suicide/suicidal thoughts or clinical worsening. Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Withdrawal symptoms, including insomnia, irritability and excessive perspiration, may occur on abrupt cessation of therapy.

The use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If administered to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge.

Cross sensitivity between nortriptyline and other tricyclic antidepressants is a possibility.

Patients with cardiovascular disease should be given nortriptyline only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia and strokes have occurred. Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

The use of nortriptyline should be avoided, if possible, in patients with a history of epilepsy. If it is used, however, the patients should be observed carefully at the beginning of treatment, for nortriptyline is known to lower the convulsive threshold.

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion and postural hypotension.

Troublesome hostility in a patient may be aroused by the use of nortriptyline.

If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy.

The possibility of a suicide attempt by a depressed patient remains after the initiation of treatment. This possibility should be considered in relation to the quantity of drug dispensed at any one time.

When it is essential, nortriptyline may be administered with electroconvulsive therapy, although the hazards may be increased.

Both elevation and lowering of blood sugar levels have been reported. Significant hypoglycaemia was reported in a Type II diabetic patient maintained on chlorpropamide (250mg/day), after the addition of nortriptyline (125mg/day).

Serotonin syndrome

Concomitant administration of Nortriptyline with buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition.

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Paediatric population

Use in children and adolescents under the age of 18:

Nortriptyline should not be used in the treatment of depression in children and adolescents under the age of 18 years. Studies in depression of this age group did not show a beneficial effect for class of tricyclic antidepressants. Studies with other classes of antidepressants (SSRIs and SNRIs) have shown risk of suicidality, self-harm and hostility to be related to these compounds. This risk cannot be excluded with nortriptyline. In addition, nortriptyline is associated with a risk of cardiovascular adverse events in all age groups. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

4.5 Drugs interactions

Gabapentin

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. In some of these reports, the authors considered the combination of gabapentin and opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those with substance abuse disorders.

In a reported study involving healthy volunteers (N=12), when a 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Co-administration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

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.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is co-administered with cimetidine is not expected to be of clinical importance.

Nortriptyline

Drug interactions: Under no circumstances should nortriptyline be given concurrently with, or within two weeks of cessation of, therapy with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions and fatalities have occurred when similar tricyclic antidepressants were used in such combinations.

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

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

Barbiturates may increase the rate of metabolism of nortriptyline.

Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the drug should be discontinued, if possible, for several days prior to the procedure, or the anaesthetist should be informed if the patient is still receiving therapy.

Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol.

The potentiating effect of excessive consumption of alcohol may lead to increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued.

Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 isoenzyme system, concomitant therapy with drugs also metabolised by this system may lead to drug interactions. Lower doses than are usually prescribed for either the tricyclic antidepressant or the other drug may therefore be required.

Greater than two-fold increases in previously stable plasma levels of nortriptyline have occurred when fluoxetine was administered concomitantly. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4-16 days for norfluoxetine).

Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (eg, quinidine), should be approached with caution.

Supervision and adjustment of dosage may be required when nortriptyline is used with other anticholinergic drugs.

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

Nortryptiline should be used cautiously when co-administered with buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased.

4.6 Use in special populations

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely.

It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

Gabapentin crosses the human placenta.

There are no or limited amount of data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is causally associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

The safety of nortriptyline for use during pregnancy has not been established, nor is there evidence from animal studies that it is free from hazard; therefore the drug should not be administered to pregnant patients or women of childbearing age unless the potential benefits clearly outweigh any potential risk.

Breast-feeding

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Nortriptyline is contra-indicated for the nursing mother and for children under the age of six years.

Fertility

There is no effect on fertility in animal studies.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms.

Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

Nortriptyline has moderate influence on the ability to drive and use machines.

Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore the patient should be warned accordingly.

4.8 Undesirable effects

Gabapentin

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (> 1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10,000; <1/1,000); very rare (<1/10,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from the post-marketing experience are included as frequency 'Not known' (cannot be estimated from the available data) in italics in the list below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Adverse drug reactions**
Infections and infestations	
Very Common	viral infection
Common	pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	
Common	leucopenia
Not known	*Thrombocytopenia*
Immune system disorders	
Uncommon	allergic reactions (e.g. urticaria*)*
Not known	*hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis (see section 4.4)*
Metabolism and nutrition disorders	
Common	anorexia, increased appetite
Uncommon	hyperglycaemia (most often observed in patients with diabetes)
Rare	hypoglycaemia (most often observed in patients with diabetes)
Not known	*hyponatraemia*
Psychiatric disorders	
Common	hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon	agitation
Not known	hallucinations, suicidal ideation
Nervous system disorders	
Very Common	somnolence, dizziness, ataxia
Common	convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia,

	headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	hypokinesia, mental impairment
Rare	loss of consciousness
Not known	*other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)*
Eye disorders	
Common	visual disturbances such as amblyopia, diplopia
Ear and labyrinth disorders	
Common	vertigo
Not known	*tinnitus*
Cardiac disorders	
Uncommon	palpitations
Vascular disorders	
Common	hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare	respiratory depression
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Uncommon	dysphagia
Not known	*pancreatitis*
Hepatobiliary disorders	
Not known	*hepatitis, jaundice*
Skin and subcutaneous tissue disorders	
Common	facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	*Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)*
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	*rhabdomyolysis, myoclonus*
Renal and urinary disorder	
Not known	*acute renal failure, incontinence*
Reproductive system and breast disorders	
Common	impotence
Not known	*breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)*
General disorders and administration site conditions	

Very Common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalized oedema
Not known	*withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.*
Investigations	
Common	WBC (white blood cell count) decreased, weight gain
Uncommon	elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known	*blood creatine phosphokinase increased*
Injury, poisoning and procedural complications	
Common	accidental injury, fracture, abrasion
Uncommon	fall

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear.

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children.

Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

Nortriptyline

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

The undesirable effects are listed according to the frequency: Not known (cannot be estimated from the available data).

System organ class	Undesirable effects
Blood and lymphatic system disorders	Bone-marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia.
Immune system disorders	Rash, petechiae, urticaria, itching, photosensitisation (avoid excessive exposure to sunlight); oedema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.
Endocrine disorders	Gynaecomastia in the male; syndrome of inappropriate secretion of antidiuretic hormone.
Psychiatric disorders	Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, drowsiness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis; increased or decreased libido, impotence. Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment

	discontinuation
Nervous system disorders	Numbness, tingling, paraesthesia of extremities; in co-ordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus; dizziness; headache. Anticholinergic effects: Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.
Cardiac disorders	Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.
Vascular disorders	Flushing
Gastrointestinal disorders	Nausea and vomiting, anorexia, epigastric distress, diarrhoea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus parotid swelling
Hepatobiliary disorders	Jaundice (simulating obstructive), altered liver function; hepatitis and liver necrosis
Skin and subcutaneous tissue disorders	Alopecia
Renal and urinary disorders	Nocturia; urinary frequency
Reproductive system and breast disorders	Breast enlargement and galactorrhoea in the female; testicular swelling;
Investigations	Elevation or depression of blood sugar levels; weight gain or loss
General disorders and administration site conditions	Sweating; weakness, fatigue; alopecia.

Withdrawal symptoms: Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

Class Effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Gabapentin

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea.

All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is usually not required.

However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000mg/kg.

Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

Nortriptyline:

Symptoms: 50mg of a tricyclic antidepressant can be an overdose in a child. Of patients who are alive at presentation, mortality of 0-15% has been reported. Symptoms may begin within several hours and may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, fever, rapid heart rate, decreased bowel sounds, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobinuric renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension and cardiac arrhythmias. Cardiac conduction may be slowed, with prolongation of QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmias (including Torsade de pointes and fibrillation) and death. Prolongation of QRS duration to more than 100msec is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilatation, central and peripheral alpha-adrenergic blockade and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient survived 5 hours of cardiac massage.

Management: Symptomatic and supportive therapy is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate. Serum electrolytes should be monitored and managed. Refractory arrhythmias may respond to propranolol, bretylium or lignocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.

Seizures may respond to diazepam. Phenytoin may treat seizures and cardiac rhythm disturbances. Physostigmine may antagonise atrial tachycardia, gut immotility, myoclonic jerks and somnolence. The effects of physostigmine may be short-lived.

Diuresis and dialysis have little effect. Haemoperfusion is unproven. Monitoring should continue, at least until the QRS duration is normal.

5. Pharmacological properties

5.1 Mechanism of action

Gabapentin

Mechanism of action

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.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the α2δ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centres through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

Nortriptyline

Nortriptyline is a tricyclic antidepressant with actions and uses similar to these of Amitriptyline. It is the principal active metabolite of Amitriptyline.

5.2 Pharmacodynamics properties

Gabapentin

Clinical efficacy and safety

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). The data from this additional post-hoc analysis are summarised in the table below:

Response (≥ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

Nortriptyline

In the treatment of depression Nortriptyline is given by mouth as the hydrochloride in doses equivalent to Nortriptyline 10 mg 3 or 4 times daily initially, gradually increased to 25 mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10 mg thrice daily. Inappropriately high plasma concentrations of Nortriptyline have been associated with deterioration in antidepressant response. Since Nortriptyline has prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

Paediatric population: Available trial data from small randomised controlled trials in major depressive disorder do not support use in children. Efficacy and safety have not been

demonstrated.

5.3 Pharmacokinetic properties

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.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2µg/ml and 20µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300mg (N = 7)		400mg (N = 14)		800mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{max} (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

C_{max} = Maximum steady state plasma concentration
t_{max} = Time for C_{max}
T1/2 = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

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.

Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites). N-oxidation and conjugation with glucuronic acid.

Excretion:

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.

Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended.

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

In a reported pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower Cmax and higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

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

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000mg/kg/day and to rats at 250, 1000, and 2000mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000mg/kg/day are 10 times higher than plasma concentrations in humans given 3600mg/day. The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic in vitro in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells in vitro or in vivo, and did not induce micronucleus formation in the bone marrow of hamsters.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000mg/kg (approximately five times the maximum daily human dose on a mg/m2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600mg, (four, five or eight times, respectively, the human daily dose on a mg/m2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hind limbs in rodents, indicative of foetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000mg/kg/day during organogenesis and in rats given 2000mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600mg on a mg/m2 basis.

No effects were observed in pregnant mice given 500mg/kg/day (approximately 1/2 of the daily human dose on a mg/m2 basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000mg/kg/day in a fertility and general reproduction study, 1500mg/kg/day in a teratology study, and 500, 1000, and 2000mg/kg/day in a perinatal and postnatal reported study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m2 basis.

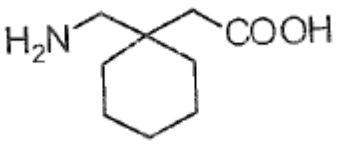
There are some reports of neurodegenerative changes in the brains of offspring exposed to gabapentin during pregnancy from rodent studies published in the open literature. However, limitations in study designs means the toxicological significance and clinical relevance of these findings are unclear. A GLP compliant perinatal and postnatal reported study in rats showed reversible behavioural changes in offspring exposed to 1000 mg/kg gabapentin (approximately 1 to 5 times the human does of 3600 mg on a mg/m2 basis) from GD15 to PND21. Overall, the available data is insufficient to determine the developmental neurotoxic potential of gabapentin.

In a reported teratology study in rabbits, an increased incidence of post-implantation foetal loss, occurred in pregnant rabbits given 60, 300, and 1500mg/kg/day during organogenesis. These doses are approximately 0.3 to 8 times the daily human dose of 3600mg on a mg/m2 basis. The margins of safety are insufficient to rule out the risk of these effects in humans.

7. Description

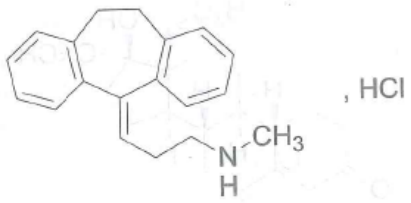
Gabapentin

Gabapentin is [1-(aminomethyl) cyclohexyl] acetic acid. The empirical formula is $C_9H_{17}NO_2$ and its molecular weight is 171.2 g/mol. The chemical structure of Gabapentin is:



Nortriptyline Hydrochloride

Nortriptyline Hydrochloride is 3-(10.11-dihydro-5H-dibenzo [a,d]cyclohept-5-ylidene)propyl(methyl)amine hydrochloride. The empirical formula is C19H21N,HCl and its molecular weight is 299.8 g/mol. The chemical structure of Nortriptyline Hydrochloride is:



GABATOR NT 100 is white coloured, round, biconvex, film coated tablets, scored on one side. The excipients used are Microcrystalline Cellulose, Lactose, Starch, PVP-K-30, Colloidal Silicone Dioxide, Magnesiun Stearate, Croscarmellose Sodium, Crospovidone, Seal Coat TR, Talcum, Super Coat Film, Titanium Dioxide, Isopropyl Alcohol.

GABATOR NT 200 is white to off white coloured, round, biconvex, film coated tablets, plain on both side. The excipients used are Starch, Microcrystalline Cellulose, Hydroxy Propyl Celloulose, Colloidal Silicone Dioxide, Magnesiun Stearate, Super Coat, Talcum, Titanium Dioxide, Isopropyl Alcohol, Methylene Chloride.

GABATOR NT 300 is white to off white coloured, elongated, biconvex, plain on both side & film coated tablet. The excipients used are Sodium Starch Glycolate, Pregelatinized Starch, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Di-Sodium Ededate, Microcrystalline Cellulose, Colloidal Silicone Dioxide, Talcum, Magnesium Stearate, Instamoist Shiled, Methylene Chloride.

GABATOR NT 400 is white colour, caplet shaped, film coated tablets having break line on one surface. The excipients used are Starch, Plasdone S-630, Polyvinyl Pyrrolidone, Pregelatinized Starch, Croscarmellose sodium, Colloidal Sillicon Dioxide, Talc, Magnesium Stearate, Protectab HP 1, Titanium Dioxide, Isopropyl alcohol and Methylene chloride.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

GABATOR NT 100, 200, 3000 is packed in blister strip of 15 tablets.

GABATOR NT 400 is packed in blister strip of 10 tablets

8.4 Storage and handing instructions

GABATOR NT 100, 200

Store below 30°C. Protected from light & moisture.

GABATOR NT 300

Store protected from Light & Moisture, at a temperature not exceeding 30°C.

GABATOR NT 400

Store in a dry place at a temperature not exceeding 30°C. Protect from light.

9. Patient Counselling Information

Package leaflet: Information for the user

GABATOR NT
Gabapentin & Nortriptyline Hydrochloride Tablets

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What GABATOR NT is and what it is used for

GABATOR NT is film coated tablet, contains Gabapentin & Nortriptyline Hydrochloride tablets and it is use for neuropathic pain in adults.

9.2 What you need to know before you use GABATOR NT Do not take

Do not take GABATOR NT

• if you are allergic (hypersensitive) to gabapentin, nortriptyline hydrochloride or any of the other ingredients of this medicine. An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue;
• if you have had a recent heart attack or heartbeat disorder;
• if you have severe liver disease;
• if you suffer from mania (abnormally raised mood);
• if you are breast-feeding;
• if the child is under 6 years of age;
• if you are taking, or have taken in the last two weeks, monoamine oxidase inhibitors (another type of antidepressant);
• if you are taking adrenaline-like drugs including ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine. These drugs are often contained in cough and cold remedies.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Gabapentin . if you:

• suffer from kidney problems your doctor may prescribe a different dosing schedule

• are on haemodialysis (to remove waste products because of kidney failure), tell your doctor if you develop muscle pain and/or weakness

• suffer with different types of seizures including absences.

• develop signs such as persistent stomach pain, feeling sick and being sick, contact your doctor immediately as these may be symptoms of acute pancreatitis (an inflamed pancreas)

• have nervous system disorders, respiratory disorders, or you are more than 65 years old, your doctor may prescribe you a different dosing regimen.

Cases of abuse and dependence have been reported for gabapentin from the post-marketing experience. Talk to your doctor if you have a history of abuse or dependence.

A small number of people being treated with anti-epileptics such as Gabapentin have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Important information about potentially serious reactions

A small number of people taking gabapentin get an allergic reaction or potentially serious skin reaction, which may develop into more serious problems if they are not treated. You need to know these symptoms to look out for while you are taking gabapentin.

Read the description of these symptoms in section 4 of this leaflet under 'Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious'

Talk to your doctor or pharmacist before taking Nortriptyline tablets

• if you feel suicidal or aggressive - tell your doctor;

• if you are agitated, overactive, or suffer from schizophrenia;

• if you have heart disease;

• if you have a thyroid condition;

• if you have a history of epilepsy;

• if you have high pressure in the eyes (glaucoma);

• if you have an enlarged prostate;

• if you are going to have electroconvulsive therapy (electric shock);

• if you are diabetic;

• if you are going to receive an anaesthetic, e.g. for an operation – tell your doctor;

• if you have had an allergic reaction to another tricyclic antidepressant in the past;

• if you are pregnant, think you might be pregnant or planning to become pregnant or breast-feeding you should not take Nortriptyline tablets unless your doctor tells you to.

The use of Buprenorphine together with Nortriptyline tablets can lead to serotonin syndrome, a potentially life-threatening condition (see "Other medicines and Nortriptyline tablets").

Children and adolescents

The dose depends on the body weight of your child. The treatment is started with a low initial dose which is gradually increased over a period of about 3 days. The usual dose to control epilepsy is 25-35mg per kg per day.

Gabapentin are not recommended for use in children below 6 years of age.

Nortriptyline should not be used in the treatment of depression in children and adolescents under the age of 18 years.

Other medicines and GABATOR NT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular:

• tell your doctor (or pharmacist) if you are taking or have been recently taking any medicines for convulsions, sleeping disorders, depression, anxiety, or any other neurological or psychiatric problems.

• medicines containing opioids such as morphine; if you are taking any medicines containing opioids (such as morphine), please tell your doctor or pharmacist as opioids may increase the effect of Gabapentin. In addition, combination of Gabapentin . with opioids may cause symptoms like sleepiness and/or decrease in breathing.

• antacids containing aluminium and magnesium (used to reduce stomach acid): if taken at the same time, absorption of Gabapentin. from the stomach may be reduced. It is therefore recommended that Gabapentin. are taken at least two hours after taking an antacid.

Urine Tests

Gabapentin . may interfere with urine tests. If you require a urine test, tell your doctor or hospital that you are taking Gabapentin.

Other medicines and Nortriptyline tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following medicines may interact with your Nortriptyline tablets:

• guanethidine, debrisoquine, bethanidine, clonidine (used to treat high blood pressure);

• barbiturates (used for anxiety or to make you feel sleepy);

• alcohol (you should not drink alcohol);

• fluoxetine (another antidepressant);

• cimetidine (for heartburn and ulcers);

• phenothiazines (for mental illness);

• carbamazepine (for epilepsy);

• propafenone, flecainide, encainide, quinidine (for heartbeat disorders);

• valproic acid (medicine used for the treatment of epilepsy and bipolar disorder).

• buprenorphine/opioids: These medicines may interact with Nortriptyline tablets and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.

It may still be all right for you to be given Nortriptyline tablets. Your doctor will be able to decide what is suitable for you.

Gabapentin with food

Gabapentin can be taken with or without food.

Pregnancy

• If you are pregnant or think you may be pregnant, you must tell your doctor straight away and discuss possible risks the medicine you are taking might pose to your unborn baby

• If you are planning to become pregnant you should discuss your treatment with your doctor as early as possible before you become pregnant

• You should not stop your treatment without discussing this with your doctor.

Gabapentin . should not be taken during pregnancy, unless you are told otherwise by your doctor. The safety of nortriptyline for use during pregnancy has not been established.

Effective contraception must be used by women of child-bearing potential.

There have been very few studies specifically looking at the use of gabapentin in pregnant women. More research is needed to better understand about the safety of use of gabapentin during pregnancy and whether it is associated with an increased risk of harm to the unborn child.

Some medicines used to treat epilepsy have reported an increased risk of harm to the developing baby, particularly when more than one seizure medication is taken at the same time. This means that where possible, your doctor should consider using one epilepsy medicine to control your epilepsy.

Fertility

There is no effect on fertility in animal studies. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding

Gabapentin is passed on through human milk. Because the effect on the baby is unknown, it is not recommended to breast-feed while using Gabapentin. Do not take Nortriptyline tablets if you are breast-feeding.

Driving and using machines

Nortriptyline tablets may affect alertness. Use caution when driving or operating heavy machinery until you're aware of how this drug affects you. If you feel Nortriptyline tablets affect your ability to drive or use machines, tell your doctor immediately.

When taking Gabapentin you may become drowsy, dizzy or feel tired, especially at the start of treatment or after a dose increase. Make sure you are not affected before driving, operating machinery or taking part in other potentially hazardous activities.

9.3 How to use GABATOR NT

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Gabapentin are usually taken three times a day (morning, afternoon and evening). Always swallow the tablet whole with plenty of water, with or without food. Your doctor will determine what dose is appropriate for you. If you are an elderly patient (over 65 years old), have kidney disease or are having haemodialysis, you should take Gabapentin as prescribed by your doctor. Continue taking Gabapentin until your doctor tells you to stop.

If you take more GABATOR NT than you should

If you or someone else accidentally takes too many or if you think a child has swallowed any, contact your doctor or go to your nearest hospital casualty department immediately. As Gabapentin may make you drowsy, it is recommended that you ask someone else to drive you to the doctor or hospital, or that you call an ambulance. Symptoms of an overdose are dizziness, double vision, slurred speech, drowsiness or tiredness, loss of consciousness

and mild diarrhoea. Overdose of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

If you forget to take GABATOR NT

Take the next dose on time. If you miss a dose, take it as soon as you remember, unless it is time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking GABATOR NT

Do not stop taking this medicine suddenly, as your symptoms may get worse. Your doctor will reduce the dose gradually, you may experience anxiety, difficulty sleeping, feeling sick, pain, sweating.

9.4 Possible Side Effects

Gabapentin

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious:

Rare (may affect up to 1 in 1,000 people):

• breathing problems, shallow breaths (respiratory depression), which if severe you may need emergency and intensive care to continue breathing normally.

Not known (frequency cannot be estimated from the available data):

• severe skin reactions that require immediate attention, swelling of the lips and face, skin rash and redness, and/or hair loss (these may be symptoms of a serious allergic reaction)

• persistent stomach pain, feeling sick and being sick as these may be symptoms of acute pancreatitis (an inflamed pancreas)

• suicidal thoughts

• anaphylaxis (serious, potentially life-threatening allergic reaction including difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment)

• Gabapentin may cause a serious or life-threatening allergic reaction that may affect your skin or other parts of your body such as your liver or blood cells. You may or may not have a rash when you get this type of reaction. It may cause you to be hospitalised or to stop Gabapentin.

Nortriptyline

Tell your doctor or pharmacist immediately if you experience any of the following serious side effects:

• sudden chest pain which may spread to the neck or arm, with a shortness of breath and a clammy feeling (these may be signs of a heart attack)

• sudden collapse, numbness or weakness in the arms or legs, headache, dizziness and confusion, disturbances in vision, difficulty swallowing, slurred, mixed up or loss of speech (these may be signs of a stroke)

• inflammation of the liver, yellowing of your skin or whites of your eyes, dark urine, pale stools, tiredness, fever, nausea, weakness, drowsiness and abdominal pain, with test results showing abnormal liver function

• thoughts of harming or killing yourself at any time.

• persistent constipation with a swollen stomach, fever and vomiting. These symptoms may be due to parts of the intestine becoming paralysed.

• bruising, bleeding, pallor or persistent sore throat and fever. These symptoms can be the first signs that your blood or bone marrow may be affected. Effects on the blood could be a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting).

The following side effects have been reported (Not known: frequency cannot be estimated from the available data):

• low or high blood pressure

• fast or irregular heartbeat

• palpitations

• oedema (swelling of the ankles)

• confusion (especially in the elderly) with seeing or hearing things (hallucinations)

• not knowing where you are (disorientation)

• false beliefs (delusions)

• anxiety, restlessness, agitation

• not sleeping (insomnia)

• nightmares

• panic

• long-lasting abnormal mood

• worsening of mental illness

• numbness, tingling, pins and needles in the hands or feet

• coordination problems

• tremors

• abnormal movements

• fits (seizures)

• altered brainwave (EEG) patterns

• ringing in the ears (tinnitus)

• dry mouth

• rarely, inflamed glands under the tongue or inflammation of the gums (gingivitis)

• blurred vision, difficulty in focusing, dilated pupils

• unable to urinate or delayed urination

• rash

• itching

• light sensitivity

• swelling (oedema)

• fever

• reaction to other similar drugs

• feeling sick (nausea) and vomiting

• not eating (anorexia)

• indigestion

• diarrhoea

• constipation.

• peculiar taste

• inflamed mouth

• abdominal cramps

• black tongue

• development of breasts in men, breast enlargement and milk production in women

• increased or decreased sex drive

• failure to have an erection (impotence)

• swollen testicles

• altered blood sugar levels

• weight gain or loss

• sweating

• flushing

• urinating often and at night

• sleepiness

• dizziness

• weakness

• tiredness

• headache

• swollen glands

• hair loss (alopecia).

• An increased risk of bone fractures has been observed in patients taking this type of medicine.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store GABATOR NT

GABATOR NT 100, 200

Store below 30°C. Protected from light & moisture.

GABATOR NT 300

Store protected from Light & Moisture, at a temperature not exceeding 30°C.

GABATOR NT 400

Store in a dry place at a temperature not exceeding 30°C. Protect from light.

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

GABATOR NT contain active substance Gabapentin & Nortriptyline Hydrochloride Tablets.

GABATOR NT 100

The excipients used are Microcrystalline Cellulose, Lactose, Starch, PVP-K-30, Colloidal Silicone Dioxide, Magnesiun Stearate, Croscarmellose Sodium, Crospovidone, Seal Coat TR, Talcum, Super Coat Film, Titanium Dioxide, Isopropyl Alcohol.

GABATOR NT 200

The excipients used are Starch, Microcrystalline Cellulose, Hydroxy Propyl Celloulose, Colloidal Silicone Dioxide, Magnesiun Stearate, Super Coat, Talcum, Titanium Dioxide, Isopropyl Alcohol, Methylene Chloride.

GABATOR NT 300

The excipients used are Sodium Starch Glycolate, Pregelatinized Starch, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Di-Sodium Ededate, Microcrystalline Cellulose, Colloidal Silicone Dioxide, Talcum, Magnesium Stearate, Instamoist Shiled, Methylene Chloride.

GABATOR NT 400

The excipients used are Starch, Plasdone S-630, Polyvinyl Pyrrolidone, Pregelatinized Starch, Croscarmellose sodium, Colloidal Sillicon Dioxide, Talc, Magnesium Stearate, Protectab HP 1, Titanium Dioxide, Isopropyl alcohol and Methylene chloride.

GABATOR NT is packed in blister strip of 15 tablets.

GABATOR NT 400 is packed in blister strip of 10 tablets.

10 Details of manufacturer

GABATOR NT 100 & 200

M/s. Synokem Pharmaceuticals Ltd.

Plot No. 56-57, Sector - 6A,

I.I.E. (SIDCUL), Ranipur (BHEL),

Haridwar – 249403 (Uttarakhand)

GABATOR NT 300

M/S Pure & Cure Healthcare Pvt. Ltd.

Plot No. 26A, 27-30, Sector-8A,

I.I.E., SIDCUL, Ranipur,

Haridwar-249 403 (Uttarakhand).

GABATOR NT 400

M/S Sunglow Lifescience Private Limited

S.No. 208/1A, 208/2A1B,

220/3B, Nelvoy-Thirumukkoodal Road,

Kattankulam Village, Uthiramerur,

Kancheepuram – 631 606

11 Details of permission or licence number with date

GABATOR NT 100 & 200

27/UA/2018 issued on 22.11.2018

GABATOR NT 300

31/UA/2013 issued on 07.12.2021

GABATOR NT 400

TN00004555 issued on 15.12.2017

12 Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ GABATOR NT 100, 200, 300 &400/AUG-2022/01/PI