Summary of product characteristics

1. Name of the medicinal product
NORBALIN
Pregabalin 75 mg and Nortriptyline 10 mg Tablets.

2. Qualitative and quantitative composition
Each Film Coated Tablet Contains: Pregabalin BP……75 Mg Nortriptyline Hydrochloride BP Eq. to Nortriptyline 10 Mg
Excipients q.s
Color: Erythrosine and Titanium Dioxide BP

3. Pharmaceutical form
Pink colored round biconvex film coated tablet having on one break line and other side plain
Excipients with known effect:
Each 10 mg tablet contains Lactose Monohydrate
For the full list of excipients, see section 6.1

4. Clinical particulars
4.1 Therapeutic indications Indicated in treatment of:
- Diabetic Peripheral Neuropathy
- Low Back Pain
- Post Herpetic Neuralgia
- Fibromyalgia
- Spinal Cord Injury pain

4.2 Posology and method of administration
Recommended oral dose of Pregared NT Tablets is twice a day. It is advised to consult doctor for the dosage, as the frequency also depends on the patient's condition.

Nortriptyline
Adults: The usual adult dose is 25mg three or four times daily. Dosage should begin at a low level e.g. 10mg three or four times daily, and be increased as required. Alternatively, the total daily dose may be given once a day, usually given at night. 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. 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.
The elderly: 30 to 50mg/day in divided doses. Dosage should begin at a low level (10 – 20 mg daily) and be increased as required to the maximum dose of 50mg. If it is considered necessary to use higher dosing in an elderly patient an ECG should be checked and plasma levels of nortriptyline should be monitored.
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.
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.
Cytochrome P450 isoenzyme CYP2D6 and poor metabolisers
Many antidepressants (tricyclic antidepressants, including nortriptyline, selective serotonin re-uptake inhibitors and others) are metabolised by the hepatic cytochrome P450 isoenzyme CYP2D6. 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.
Reduced renal function
Renal failure does not affect kinetics of nortriptyline. This medicinal product can be given in usual doses to patients with renal failure.
Reduced hepatic function
In case of reduced liver function careful dosing and, if possible, a serum level determination is advisable.
Paediatric population
Nortriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section 4.4).
Duration of treatment
The antidepressant effect usually sets in after 2 - 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.
Discontinuation of treatment
When stopping therapy nortriptyline should be gradually withdrawn over several we
Pregabalin.
The dose range is 150 to 600 mg per day given in either two or three divided doses.
Neuropathic pain

Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

Epilepsy

Pregabalin treatment can be started with a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.

Generalised anxiety disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see sections 4.4 and 4.8).

Renal impairment

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance (see section 5.2), dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in Table 1 determined using the following formula:

$$CL_{cr}(ml/min) = \frac{1.23 \times [140 - age\ (years)] \times weight\ (kg)}{serum\ creatinine\ (\mu mol/l)} \quad (\times 0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4 hour haemodialysis treatment (see Table 1).

Table 1. Pregabalin Dose Adjustment Based on Renal Function

Creatinine clearance (CL_{cr}) (mL/min)	**Total pregabalin daily dose***		**Dose regimen**
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25-50	150	Once Daily or BID

< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen provide mg/dose
+ Supplementary dose is a single additional dose

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Pregabalin Amarox in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see section 5.2).

Method of administration

For oral use.

4.3 Contraindications

Pregared NT Tablets is contraindicated in patient with hypersensitivity to any component of tablets and history of urinary retention – BPH

4.4 Special warnings and precautions for use

Do not drink alcohol while taking Pregared NT Tablets. It can increase the effects of alcohol, which could be dangerous.

• Grapefruit and grapefruit juice may also interact with this medicine and cause unwanted side effects.

• Use of Pregared NT tablets can make patient more prone to sunburns. Hence avoid exposure to sunlight or tanning beds. Wear protective clothing and use sunscreen when outdoors during daytime.

Nortriptyline.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5).

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

Treatment with nortriptyline 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 nortriptyline.

- Recent myocardial infarction, any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency
Pregabalin

4.5 Interaction with other medicinal products and other forms of interaction

Nortriptyline

Some products that may interact with Nortriptyline include: arbutamine, "blood thinners" (such as warfarin), disulfiram, thyroid supplements, anticholinergic drugs (such as benztropine, belladonna alkaloids), certain drugs for high blood pressure (drugs that work in the brain such as clonidine, guanabenz).

Taking MAO inhibitors with Nortriptyline may cause a serious (possibly fatal) drug interaction. Avoid taking MAO inhibitors (isocarboxazid, linezolid, methylene blue, moclobemide, phenelzine, procarbazine, rasagiline,safinamide,selegiline, tranylcypromine) during treatment with this medication.

The risk of serotonin syndrome/toxicity increases if taken with other drugs that increase serotonin. Examples include street drugs such as MDMA/"ecstasy," St. John's wort, certain antidepressants (including SSRIs such as fluoxetine/paroxetine, SNRIs such as duloxetine/venlafaxine), among others.

Other medications can affect the removal of nortriptyline from body, thereby affecting how nortriptyline works. These drugs include cimetidine, terbinafine, drugs to treat irregular heart rate (such as quinidine/propafenone/flecainide).

Contraindicated combinations

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) - risk of “serotonin syndrome” (see section 4.3).

Combinations that are not recommended

Sympathomimetic agents

Nortriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine **(e.g. as contained in local and general anaesthetics and nasal decongestants)**.

Adrenergic neurone blockers/antihypertensives

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.

Anticholinergic agents

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 (see section 4.4).
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
CNS depressants: Nortriptyline may enhance the sedative effects of alcohol, **barbiturates and other CNS depressants.**
Tricyclic antidepressants (TCA) including nortriptyline are primarily metabolised by various hepatic cytochrome P450 isozymes (e.g., CYP1A2, CYP2C, CYP2D6, CYP3A4).
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 (see section 4.2).
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.
Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.
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.

In the presence of ethanol nortriptyline plasma concentrations were increased.
The CYP3A4 and CYP1A2 isozymes metabolise nortriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase nortriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of nortriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.
Nortriptyline plasma concentration can be increased by valproic acid. Clinical monitoring is therefore recommended.

Pregabalin
Pregabalin has no known severe interactions with other drugs. Serious interactions of Pregabalin include:
Benazepril, Captopril,Enalapril,Everolimus,Fosinopril,Imidapril,Lisinopril Moexipril,Perindopril,Quinapril,Ramipril,Sirolimus Temsirolimus,trandolapril.
Moderate interactions of Pregabalin include:clobazam,deutetrabenazine,lurasidone,orlistat
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.
In vivo studies and population pharmacokinetic analysis
Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.
Oral contraceptives, norethisterone and/or ethinyl oestradiol
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.
Central nervous system influencing medical products
Pregabalin may potentiate the effects of ethanol and lorazepam.
In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.
Interactions and the elderly
No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
Pediatric:
safety and efficacy has not been evaluated in children.

Geriatric:
safety and efficacy has not been evaluated in old patients.
Liver impairment:
Not recommended.
Renal failure:
Use with caution.
Pregnancy and lactation:
Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nortriptyline

Pregnancy
There is a moderate amount of data from the use of nortriptyline in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Therefore, the drug should not be administered to pregnant patients or women of childbearing age unless the potential benefits clearly outweigh any potential risk.
Following administration in the final weeks of pregnancy, neonatal withdrawal symptoms **may occur including** irritability, hypertonia, tremors, irregular breathing, weak suckling and possibly anticholinergic symptoms (urine retention, obstipation).
Breast-feeding
Nortriptyline is excreted in limited amounts in breastmilk (corresponding to 0.6 % - 1 % of the maternal dose). Adverse effects for infants have not been reported thus far. Breastfeeding can be continued during nortriptyline therapy if the benefit of the mother outweighs the potential risk for the infant. Observation of the infant is advised, especially during the first four weeks after birth.
Fertility
The reproductive toxicity of nortriptyline has not been investigated in animals. For its parent substance amitriptyline, association with an effect on fertility in rats, namely a lower pregnancy rate was observed. (see section 5.3).

Pregabalin

Women of childbearing potential/ Contraception
Women of childbearing potential have to use effective contraception during treatment (see section 4.4).
Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3).
Pregabalin has been shown to cross the placenta in rats (see section 5.2).
Pregabalin may cross the human placenta.
Major congenital malformations
Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).

The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)).
The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise.
Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).
Breast-feeding
Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Fertility
There are no clinical data on the effects of pregabalin on female fertility.
In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.
A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

NORBALIN Tablets may impair thinking or reactions. Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Pregared NT Tablets is known.

4.8 Undesirable effects

- Sedation, Drowsiness and Dizziness
- Weight Gain
- Dry mouth, blurred vision, increased intraocular pressure, constipation
- Hypotension, Syncope, Palpitations, Myocardial Infarction & Arrhythmias

Nortriptyline.

in the listing below the following convention is used:
MedDRA system organ class / preferred term
Very common (≥ 1/ 10); common (≥ 1/ 100 to <1/ 10); uncommon (≥ 1/ 1,000 to <1/ 100); rare (≥ 1/ 10,000 to <1/ 1,000); very rare (<1/ 10,000).not known (cannot be estimated from the available data).

MedDRA SOC	***Frequency***	***Preferred Term***
Blood and lymphatic system disorders	*Rare*	*Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia.*
Endocrine disorders	*Not Known*	*Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)*

Metabolism and nutrition disorders	*Rare*	*Decreased appetite.*
	Not Known	*changes of blood sugar levels*
Psychiatric disorders	*Very common*	*aggression*
	Common	*Confusional state, libido decreased, agitation*
	Uncommon	*Hypomania, mania, anxiety, insomnia, nightmare.*
	Rare	*Delirium (in elderly patients), hallucination (in schizophrenic patients).*
	Not Known	**Suicidal ideation and suicidal behaviour, paranoia*
Nervous system disorders	*Very common*	*Tremor, dizziness, headache.*
	Common	*Disturbance in attention, dysgeusia, paresthesia, ataxia.*
	Uncommon	*Convulsion.*
	Rare	*akathisia, dyskinesia*
	Not Known	*Extrapyramidal disorder*
Eye disorders	*Very common*	*Accommodation disorder.*
	Common	*Mydriasis.*
	Very rare	*Acute glaucoma*
Ear and labyrinth disorders	*Uncommon*	*Tinnitus.*
Cardiac disorders	*Very common*	*Palpitations, tachycardia*
	Common	*Atrioventricular block, bundle branch block.*
	Uncommon	*Collapse conditions, worsening of cardiac failure*
	Rare	*Arrhythmia.*
	Very rare	*Cardiomyopathies, torsades de pointes*
	Not Known	*hypersensitivity myocarditis*
Vascular disorders	*Common*	*Orthostatic hypotension.*
	Uncommon	*Hypertension*
	Not known	*Hyperthermia*
Respiratory, thoracic, and mediastinal disorders	*Very common*	*Congested nose.*
	Very rare	*Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome)*
Gastrointestinal disorders	*Very common*	*Dry mouth, constipation, nausea.*
	Uncommon	*Diarrhoea, vomiting, tongue oedema.*
	Rare	*Salivary gland enlargement, ileus paralytic.*

Hepatobiliary disorders	*Uncommon*	*Hepatic impairment (e.g. cholestatic liver disease).*
	Rare	*Jaundice.*
	Not Known	*Hepatitis*
Skin and subcutaneous tissue disorders	*Very common*	*Hyperhidrosis.*
	Uncommon	*Rash, urticaria, face oedema.*
	Rare	*Alopecia, photosensitivity reaction.*
Renal and urinary disorders	*Uncommon*	*Urinary retention.*
	Common	*Micturition disorders*
Reproductive system and breast disorders	*Common*	*Erectile dysfunction.*
	Uncommon	*Galactorrhoea.*
	Rare	*Gynaecomastia*
General disorders and administration site conditions	*Common*	*Fatigue, feeling thirst*
	Rare	*Pyrexia.*
Investigations	*Very common*	*Weight increase*
	Common	*Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia.*
	Uncommon	*Intraocular pressure increased.*
	Rare	*Weight decreased.* *Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased.*

**Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early after treatment discontinuation (see section 4.4)*

Withdrawal symptoms:

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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.co.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Pregabalin

The pregabalin clinical programme involved over 8,900 patients exposed to pregabalin, of whom over 5,600 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and

somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.
In table 2 below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicinal products.
In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased (see section 4.4).
Additional reactions reported from postmarketing experience are included in italics in the list below.

Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	*Hypersensitivity*
Rare	Angioedema, allergic reaction
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, suicidal behaviour, suicidal ideation
Not known	Drug dependence
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy

Uncommon	Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise
Rare	Convulsions, parosmia, hypokinesia, dysgraphia, parkinsonism
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure
Rare	QT prolongation, sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	Pulmonary oedema, throat tightness
Not known	Respiratory depression
Gastrointestinal disorders	
Common	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, swollen tongue, dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, pruritus
Rare	Stevens-Johnson syndrome, cold sweat, Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm

Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, urinary retention
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, gynaecomastia
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness. These symptoms may indicate drug dependence. The patient should be informed about this at the start of the treatment. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related (see sections 4.2 and 4.4).

Paediatric population

The pregabalin safety profile observed in five paediatric studies in patients with partial seizures with or without secondary generalisation (12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study, n=65; and two 1 year open label follow on safety studies, n=54 and n=431) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia (see sections 4.2, 5.1 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

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

Nortriptyline

Signs and 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.

Treatment: 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 Pharmacodynamic properties

Pharmacotherapeutic group:

Pregabalin: Antiepileptics, other antiepileptics ATC code: N03AX16
Nortriptyline: Antidepressants, ATC code: N06AA10
Mechanism of action
It is believed that nortriptyline either inhibits the reuptake of the neurotransmitter serotonin at the neuronal membrane or acts at beta-adrenergic receptors. It displays a more selective reuptake inhibition for noradrenaline, which may explain the relief and improvement of biological symptoms with nortriptyline therapy. Tricyclic antidepressants do not inhibit monoamine oxidase nor do they affect dopamine reuptake. As with other TCAs, nortriptyline displays affinity for other receptors including mACh receptors, histamine receptors and 5-HT receptors. Antimuscarinic effects upon binding to mAChR are responsible for various side effects of TCAs.
By binding presynaptically to the alpha2-delta subunit of voltage-gated calcium channels in
the central nervous system, Pregabalin modulates the release of several excitatory neurotransmitters including glutamate, substance-P, norepinephrine, and calcitonin gene related peptide. In addition, Pregabalin prevents the alpha2-delta subunit from being trafficked from the dorsal root ganglia to the spinal dorsal horn, which may also contribute to the mechanism of action. Although Pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA or benzodiazepine receptors.

5.2 Pharmacokinetic properties
Absorption As with other TCAs, notriptyline is well absorbed from the GI tract. Peak plasma concentrations occur within 4-8.8 hours following oral administration, with the mean time of 5.5 hours. The mean oral bioavailability is 51% Protein binding Plasma protein binding is approximately 93% Metabolism Nortriptyline undergoes hepatic metabolism via the same pathway as other TCAs, where it is metabolized via demethylation and hydroxylation followed by conjugation with glucuronic acid. The metabolism is subject to genetic polymorphism (CYP2D6). The main active metabolite is 10-hydroxynortriptyline exists in a cis and a trans form, where the trans form is dominant and more pharmacologically potent. N-demethylnortriptyline is also formed to some extent. The metabolites have the same pharmacological profile as nortiptyline, but are weaker. 10-hydroxynortriptyline dominates in the plasma, but most of the metabolites are conjugated Excretion Nortriptyline and its
metabolites are mainly excreted in the urine, where only small amounts (2%) of the total drug is recovered as unchanged parent compound .
Approximately one-third of a single orally administered dose is excreted in urine within 24 hours. Small amounts are excreted in feces via biliary elimination.
• **Pregabalin**
Absorption After oral dosing administered in the fasted state, pregabalin absorption is rapid, and extensive. Pregabalin oral bioavailability is reported to be ≥90% regardless of the dose. Cmax is attained within 1.5 hours after single or multiple doses, and steady state is attained within 24-48 hours

with repeated administration. Both Cmax and AUC appear to be dose proportional. Protein binding Pregabalin is not plasma protein bound. Metabolism Less than 2% of pregabalin is metabolized and it is excreted virtually unchanged in the urine Excretion Pregabalin is almost exclusively eliminated in the urine

5.3 Preclinical safety data

Nortriptyline inhibits ion channels, which are responsible for cardiac conduction (SCN5A- and hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, nortriptyline may increase the risk for cardiac arrhythmia (see section 4.4).
Nortriptyline did not show any mutagenic potential.
The reproductive toxicity of nortriptyline has not been investigated in animals. For its parent substance amitriptyline, teratogenic effects and developmental delays, such as cranial malformations and encephalocele, have been only observed at high dosages. There was also a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown.

Pregabalin

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long-term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.
Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.
Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.
Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests.
Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short-term and

limited long-term clinical data. There is no evidence to suggest an associated risk to humans.
In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

6. Pharmaceutical particulars

6.1 List of excipients

Dibasic Calcium Phosphate
Microcrystalline Cellulose ACCEL N102
Povidone K-30
Magnesium Stearate
Purified Talc
Croscarmellose sodium
Pregelatinized Starch
Colloidal Silicon Dioxide
Easy Coat white FC
Erythrosine
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage.

Do not store above 30^0c.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu - Alu Blister Pack
10 Tablets are blister packed with Aluminum - Aluminum foil; such 1 blister packed in one carton pack.
Pack size: 1 x 10 Tablets in one carton box along with packing leaflet.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
SIMBA PHARMACEUTICALS LTD.
1st Floor, Almont Park, Westlands . P.O. Box 1541-00606 Nairobi,KENYA
Telephone: 020 4452449
E-Mail: info@simbapharma.co.ke

Manufacturing site address:
Aksharam Pharma Pvt. Ltd.
Plot No,1&2, Akshar Ind, Estate, Rajkot Highway Road, Opp. Tri-Mandir,
Kherali, Dist. Surendranagar (363020), Gujarat, India
E-Mail:aksharampharma@gmail.com

8. Marketing authorization number
CTD10482

9. Date of first registration:
04/05/2023

10. date of revision of text
14/09/2023

11. dosimetry
Not Applicable

11.Instructions for Preparation of Radiopharmaceuticals
Not Applicable