SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Pregabalin & Nortriptyline Tablets (CABALIN 25 NT TABLETS)

2. Qualitative and quantitative composition

Each film coated tablet contains

Pregabalin	BP	25 mg
Nortriptyline Hydrochloride	BP	
Eq. to Nortriptyline		5 mg

Excipients……QS

Approved colour used in tablet coating

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

White, round, biconvex, plain on both side film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

CABALIN 25 NT Tablets is indicated in treatment of:

- Diabetic Peripheral Neuropathy
- Low Back Pain
- Post Herpetic Neuralgia
- Fibromyalgia
- Spinal Cord Injury

4.2 Posology and method of administration

Recommended oral dose of CABALIN 25 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.

4.3 Contraindications

CABALIN 25 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 CABALIN 25 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 CABALIN 25 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.

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). This is not a complete list.

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

4.6 Fertility, pregnancy and lactation
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.

4.7 Effects on ability to drive and use machines
CABALIN 25 NT 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 CABALIN 25 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

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 requested 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 CABALIN 25 NT. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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.

Nortriptyline is a tricyclic antidepressant of the dibenzocycloheptene type and is the active metabolite of amitriptyline. It is an inhibitor of pre-synaptic noradrenaline reuptake than of serotonin, and is less anticholinergic than amitriptyline whilst having stronger antihistaminergic effects. Nortriptyline has been observed to increase the pressor effect of norepinephrine but blocks the pressor response of phenethylamine.

Although the structure of pregabalin is similar to gamma-aminobutyric acid (GABA), it does not bind to GABA receptors. Instead, it binds the alpha2-delta subunit of presynaptic voltage-gated calcium channels in the central nervous system. Pregabalin does not modulate dopamine receptors, serotonin receptors, opiate receptors, sodium channels or cyclooxygenase activity.

5.2 Pharmacokinetic properties

Nortriptyline

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
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.
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

Core tablet

Magnesium Stearate
Purified Talc
Hydroxy Propyl Cellulose
Lactose
Colloidal Silicon Dioxide
Crospovidone
Microcrystalline Cellulose

Film coating

Hydroxy propyl methyl cellulose (E-15)
Purified Talc
Isopropyl Alcohol
Dichloromethane
Titanium Dioxide
Polyethylene Glycol (as 6000)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage
Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container
10 tablets are packed in an Alu-Alu blister and 3 such blisters are packed in a carton along with package insert.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
GALAXY PHARMACEUTICAL LTD.
1st Floor, Doctors Park, 3rd Parkland Avenue,
P.O.BOX 39107 - 00623,
Nairobi (Kenya).

Manufacturer
Saitech Medicare Pvt. Ltd.
Trilokpur road, Kala-Amb
Dist. Sirmor, Himachal Pradesh (INDIA).

8. MARKETING AUTHORIZATION NUMBER
CTD10736

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