SUMMARY PRODUCT CHARACTERISTICS:

1. Name of drug product:

Nervilin NT tablets

2. Qualitative and Quantitative Composition:

Each film coated tablet contains: Pregabalin 75mg and Nortriptyline (As Hydrochloride) 10mg
Full list of excipients see Section 6.1.

3. Pharmaceutical form:

Yellow, round, biconvex shaped film coated tablets with a break line on one side

4. Clinical particulars:

4.1 Therapeutic Indications:

Nervillin NT tablet is used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms; Seizures, Nerve damage pain, Anxiety disorders in adults, depression and bed wetting in children.

4.2 Posology and Method of Administration:

Oral administration
One tablet once or twice daily after food based on condition

4.3 Contraindications:

Nervilin NT is contraindicated in patients with:
-Hypersensitivity to the active substances or to any of the excipients.

- Acute myocardial infarction
- Bowel obstruction
- Cardiac arrhythmias
- Diabetes mellitus
- Epilepsy
- Hypersensitivity
- Hyperthyroidism
- Hypomania
- Lactation
- Liver disease
- Narrow angle glaucoma
- Peripheral edema
- Phaeochromocytoma
- Pregnancy
- Urinary retention.

4.4 Special Warnings and Precautions for Use:

-Alcohol should be avoided when taking Nervillin NT tablets

4.5 Interaction with other medicinal products, and other forms of interaction:

Since Pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that Pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between Pregabalin and commonly used antiepileptic drugs.

Pregabalin interacts with the following medications; Heart medicines, such as the angiotensin converting enzyme (ACE) inhibitors benazepril , captopril, and enalapril ; Antidepressants, Antihistamines, Tranquilizers or drugs used to treat anxiety, including lorazepam, Medications for mental illness or seizures, Certain medications for diabetes, such as pioglitazone and rosiglitazone. Narcotic pain medications including oxycodone and Sedatives or sleeping pills.

Nortriptyline hydrochloride can potentially interact with many medicines. Some of the medicines that may lead to nortriptyline interactions include: Alcohol, Anticholinergic medications, Arrhythmia medications, Barbiturates, Monoamine oxidase inhibitors (MAOIs), Phenothiazine medications, Pressors, SSRI or SNRI medications, Thyroid medications, Tramadol ,Other tricyclic antidepressants, Triptans and Tryptophan.

4.6 Pregnancy and Lactation:

Pregnancy

Nervillin NT is not recommended during pregnancy.

Lactation

Nervillin NT is not recommended while breast-feeding.

4.7 Effects on ability to drive and use machines:

Patients should not drive, use machinery or participate in dangerous activities while taking Nervillin NT tablets.

4.8 Undesirable effects:

The most commonly reported side-effects of Nervilin NT Tablets are decrease in sexual interest, Unable to sleep, Irritability, Muscle cramps, Fatigue, and Blurred vision.

The following is a list of possible side effects that may occur from the use of Nervilin NT Tablets. This is not a comprehensive list. These side effects are possible, but do not always occur. Some of the side effects may be rare but serious.

- Decrease in sexual interest
- Unable to sleep
- Irritability
- Muscle cramps
- Fatigue
- Blurred vision

- Clumsiness
- Memory impairment
- Sore throat
- Hypersensitivity
- Joint pain
- Numbness
- Feeling of elation
- Tingling feeling
- Vomiting
- Tremor
- Drowsiness
- Increased appetite
- Dizziness
- Confusion
- Tiredness
- Urge to vomit
- Difficulty in passing stool
- Sedation
- Difficulty with speaking
- Loose motions
- Back pain
- Sleepiness
- Feeling abnormal
- Gas
- Dry mouth
- Headache
- Weight gain
- Visual disturbance
- Ataxia
- Dysarthria
- Lethargy
- Euphoria
- Constipation
- Agitation
- Peripheral oedema
- Hallucinations
- Myoclonus
- Urinary incontinence
- Dysuria
- Thrombocytopenia
- Neutropenia
- Pancreatitis
- Dysphagia
- Oliguria
- Rhabdomyolysis
- Decreased sex drive
- Ringing in the ear
- Impotence
- Weakness
- Tingling or numbness in the fingers or toes

- Nausea
- Unpleasant taste
- Lack of coordination or jerky movements
- Breast swelling in men
- Difficulty reaching orgasm after ample sexual stimulation
- Tachycardia
- Slows conduction
- Peripheral neuropathy
- Urinary hesitancy
- Sweating
- Rashes
- Hypersensitivity reactions

4.9 Overdose:

Patients with an overdose should be managed by symptomatic and supportive care.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pregabalin is an analog of the neurotransmitter GABA. It binds potently to the alpha 2-delta subunit resulting in modulation of Ca channels and reduction in the release of several neurotransmitters, including glutamate, norepinephrine, serotonin, dopamine, and substance P.

Nortriptyline is believed to either inhibit the reuptake of the neurotransmitter serotonin at the neuronal membrane or act at beta-adrenergic receptors. Tricyclic antidepressants do not inhibit monoamine oxidase nor do they affect dopamine reuptake.

5.2 Pharmacokinetic Properties:

Absorption

Pregabalin steady state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the

urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

Linearity/non-linearity

Pregabalin pharmacokinetics is linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (< 20%). Multiple dose pharmacokinetics is predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Renal impairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary.

Hepatic impairment

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Paediatric population

Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours post dose.

Pregabalin C_{max} and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied.

Elderly

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function.

Breast-feeding mothers

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

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

5.3 Pre-clinical safety data:

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, mutagenesis, impairment of fertility

In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactose monohydrate, Maize Starch, Microcrystalline cellulose, Maize Starch, Sodium Methyl paraben, Magnesium Stearate, Hypromellose 6CPS, Titanium Dioxide, Purified Talc, Yellow iron oxide, Monopropylene Glycol, Isopropyl Alcohol and Dichloromethane.

6.2 **Incompatibilities:**
None reported

6.3 **Shelf-Life:**
24 months from the date of manufacture.

6.4 **Special Precautions for Storage:**
Store in a dry place below 30^0C, protect from direct sunlight.

6.5 **Nature and Contents of Container:**
Blister pack of 3 x 10's in a unit box.

6.6 **Special precautions for disposal:**
No special requirements.

7. **Registrant:**
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9. **Date of revision of the text:**
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