AmNuring™-P
Tablets

1. **Generic name**
   Amitriptyline + Pregabalin

2. **Qualitative and Quantitative Composition**

Amitriptyline IR	10 mg
Pregabalin	75 mg

3. **Dosage form and strength**
   Oral tablets containing Amitriptyline 10mg and Pregabalin 75mg.

4. **Clinical particulars**

4.1 Therapeutic indication

AmNuring-P tablets are indicated in management of:

- Neuropathic pain associated with Diabetic Peripheral Neuropathy and Post Herpetic Neuralgia
- Pain associated with spinal cord injury.

4.2 Posology and method of administration

As directed by physician.

4.3 Contraindication

AmNuring-P tablets are contraindicated in patients with:

- Hypersensitivity to any component
- It should not be given concomitantly with a MAO inhibiting compound.
- Impaired liver function
- History of urinary retention – Benign Prostatic Hypertrophy (BPH)
- Pregnancy and Lactation

4.4 Special warnings and precautions for use

- **Clinical Worsening and Suicide Risk**

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes

in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

- Amitriptyline should be used with caution in patients with a history of seizures, impaired liver function, a history of hepatic damage or blood dyscrasias and, because of its atropine-like action, in patients with a history of urinary retention, or with narrow-angle glaucoma or increased intraocular pressure.
- In patients with narrow-angle glaucoma, even average doses may precipitate an attack.
- There has been a report of fatal dysrhythmia occurring as late as 56 hours after amitriptyline overdose. Patients with cardiovascular disorders should be watched closely.
- Tricyclic antidepressant drugs, including amitriptyline, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. A few instances of unexpected deaths have been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have also been reported with drugs of this class. Therefore, these drugs should be used with caution in patients with a history of cardiovascular disease, such as myocardial infarction and congestive heart failure.
- Close supervision is required when amitriptyline is given to hyperthyroid patients or that receiving thyroid medication.
- The potency of amitriptyline is such that addition of other antidepressant drugs generally does not result in any additional therapeutic benefit. Untoward reactions have been reported after the combined use of antidepressant agents having varying modes of activity. Accordingly, combined use of amitriptyline and other antidepressant drugs should be undertaken only with due recognition of the possibility of potentiation and with a thorough knowledge of the pharmacology of both drugs.
- There have been no reports of untoward events when patients receiving amitriptyline were changed immediately to protriptyline or vice versa. Discontinue the drug several days before elective surgery if possible.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- In accordance with current clinical practice, some diabetic patients who gain weight on treatment may need to adjust hypoglycaemic medications.
- AmNuring-P should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.
- AmNuring-P may cause dizziness and somnolence, loss of consciousness, confusion, and mental impairment.

- The increased risk of suicidal thoughts or behaviour with AEDs (Antiepileptic drugs) was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed

4.5 Drug interactions

- Amitriptyline may block the antihypertensive action of guanethidine or similarly acting compounds.
- When amitriptyline is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anaesthetics, close supervision and careful adjustment of dosage are required.
- Since amitriptyline, in combination with anticholinergic type drugs, may give rise to paralytic ileus, particularly in elderly or hospitalized patients, appropriate measures should be taken if constipation occurs in these patients.
- Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.
- Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75 to150 mg of amitriptyline.
- Amitriptyline may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.
- Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.
- Decreased GI tract absorption with neomycin, aminosalicylic acid, H2-blockers and colchicine.

4.6 Use in special population

- Paediatric: Behavioural changes have been observed in children receiving tricyclics for the treatment of enuresis.
- Geriatric: Elderly patients are particularly liable to experience adverse reactions: especially agitation, confusion and postural hypotension. In general, lower doses are recommended for elderly patients who should be increased slowly if required. The required dosage may be administered either as divided doses or as a single dose preferably in the evenings or at bedtime
- Liver impairment: Contraindicated in patients with liver impairment.
- Renal failure: Use with caution.
- Pregnancy and lactation: Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons. There is no, or inadequate evidence of safety of the drug in human pregnancy; although it has been in wide use for many years without apparent ill-consequence. There is

evidence of harmful effects in pregnancy in animals, when given in exceptionally high doses. Amitriptyline and Pregabalin both are detectable in breast milk. Because of the potential serious adverse reactions in infants from amitriptyline, a decision should be made whether to discontinue breast-feeding or discontinue the drug.

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

The adverse effects are : Anaemia, Thrombocytopenia, Tachycardia, Cardiac arrest, Hypoacusis, Tinnitus, Vertigo, Vision blurred, Vision impairment, Dry mouth, Constipation, Nausea, Vomiting, Hepatic function abnormal, Hepatitis, Drug hypersensitivity, Toxicity to various agent, Weight increased, Heart rate increased, Decreased appetite, Dizziness, Somnolence, Headache, Premature baby, Product substation issue, Completed suicide, Urinary retention, Dysuria, Respiratory arrest, Dyspnoea, Rash, Pruritis, Vascular disorder, Palpitation, Chest pain, Myocardial infraction, Anaphylactic disorder, Endocrine disorder, Malaise, Feeling abnormal, Fatigue, Gait disturbance, Withdrawal syndrome, Condition aggravated, Oedema peripheral, Asthenia, Swelling, Drug intolerance, Liver disorder, Weight decreased, Pain in extremity, Arthralgia, Back pain, Muscle spasms, Myalgia, Neoplasm malignant, Insomnia, Confusional state, Anxiety, Depression, Erectile dysfunction.

4.9 Overdose

High doses of amitriptyline may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Overdosage may cause hypothermia; drowsiness; tachycardia and other arrhythmic abnormalities such as bundle branch block; congestive heart failure; ECG evidence of impaired conduction; dilated pupils; disorders of ocular motility, convulsions; severe hypotension; stupor, coma and polyadiculoneuropathy; constipation. Other symptoms which may occur include agitation, muscle rigidity, hyperactive reflexes, hyperpyrexia, vomiting or any of the effects listed in the section on undesirable effects above. All persons suspected of having taken an overdosage should be admitted to hospital as soon as possible. Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible by emesis, followed by gastric lavage once in hospital. Following gastric lavage, oral administration of activated charcoal during the first 24 - 48 hours at a dosage of 20 - 30 g every four to six hours has been shown to reduce the delayed toxic effects due to enterohepatic circulation and slow absorption. An ECG should be taken and the cardiac function should be monitored closely if there is any sign of abnormality. An open airway and

an adequate fluid intake should be maintained; body temperature should be regulated. Physostigmine salicylate, 1-3 mg, given intravenously has been reported to reverse the symptoms of tricyclic antidepressant poisoning. Because of the rapid metabolism of physostigmine, the dosage of physostigmine should be repeated as required, particularly if lifethreatening signs such as convulsions, arrhythmias and deep coma recur or persist after the initial dose of physostigmine. Because physostigmine may itself be toxic, it is not recommended for routine use. Standard measures should be employed to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine or propranolol. If cardiac failure occurs, use of digitalis should be considered. It is advisable to closely monitor cardiac function for at least five days. If convulsions occur, they should be treated with paraldehyde, diazepam or an inhalation anaesthetic. Barbiturates should not be used because amitriptyline increases their CNSdepressant action. Dialysis is of no value in amitriptyline overdosage because of the low plasma concentrations of amitriptyline. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with tricyclic antidepressants.

Pregabalin In overdoses up to 15 g, no unexpected adverse effects were reported. If taken in overdose included affective disorder, somnolence, confusional state, depression, agitation and restlessness.

5. Pharmacological properties

5.1 Mechanism of action

Antidepressant effect of Amitriptyline is due to inhibition of reuptake of Serotonin and Norepinephrine by neuronal membranes. Earlier it was believed that the same was responsible for its analgesic action. But now it has been demonstrated due to: – Sodium channel blockade similar to local anaesthetic. – Blockade of Serotonin Receptors - 5-HT2A, 5-HT2C, 5-HT3, 5-HT6 & 5-HT7 – Inhibition of Nicotinic Acetylcholine Receptors.

Pregabalin binds presynaptically to the alpha2-delta subunit of the voltage-gated calcium channels in central nervous system tissues located in the brain and spinal cord. The mechanism of action has not been fully elucidated but studies suggest that pregabalin produces a disruption of calcium channel trafficking or a reduction of calcium currents. The inhibition of subunits of voltage-gated calcium channels reduces calcium release which in turn inhibits the release of several neurotransmitters. Studies also suggest that the descending noradrenergic and serotonergic pathways originating from the brainstem may be involved with the mechanism of Pregabalin. Interestingly, although Pregabalin is a structural derivative of inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA or benzodiazepine receptors

5.2 Pharmacodynamic properties

Amitriptyline, a tertiary amine tricyclic antidepressant, is structurally related to both the skeletal muscle relaxant cyclobenzaprine and the thioxanthene antipsychotics such as thiothixene. It is extremely sedating, and thus improvement of sleep patterns can be the first benefit of treatment. Amitriptyline exhibits strong anticholinergic activity, cardiovascular effects including orthostatic hypotension, changes in heart rhythm and conduction, and a lowering of the seizure threshold. As with other antidepressants, several weeks of therapy may be required in order to realize the full clinical benefit of amitriptyline. Although not a labelled indication, amitriptyline is widely used in the management of chronic nonmalignant pain (e.g., post-herpetic neuralgia, fibromyalgia).

Pregabalin is a structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). It has been reported that its action presents the function of modulating the release of many excitatory neurotransmitters such as glutamate, norepinephrine, substance-P and calcitonin gene related peptide. This modulation can cause an inhibitory modulation of overexcited neurons allowing them to get back to a normal state, including the decrease on the hyper excitability caused by tissue damage. The neurotransmitter modulation allows Pregabalin to present antiallodynic, anxiolytic and anticonvulsant activity

5.3 Pharmacokinetic properties

Amitriptyline is readily absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 6 hours after oral doses. Amitriptyline undergoes extensive first-pass metabolism and is demethylated in the liver by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6 to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation (possibly to active metabolites) by CYP2D6 and N-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form. Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have an elimination half-life ranging from about 9 to 25 hours, which may be considerably extended in overdosage. Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established. Amitriptyline and nortriptyline cross the placenta and are distributed into breast milk.

Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations are achieved within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by haemodialysis. Distribution into milk has been found in studies in rats.

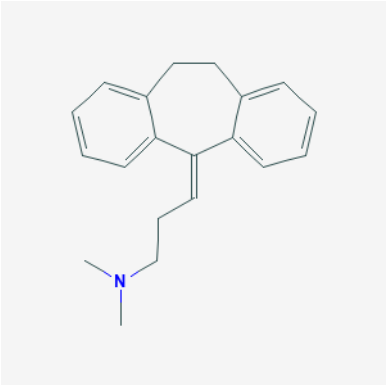
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Not required.

7. Description

Amitriptyline: Amitriptyline is a derivative of dibenzocycloheptadiene and a tricyclic antidepressant. Amitriptyline inhibits the re-uptake of norepinephrine and serotonin by the presynaptic neuronal membrane in the central nervous system (CNS), thereby increasing the synaptic concentration of norepinephrine and serotonin. Due to constant stimulation to these receptors, amitriptyline may produce a downregulation of adrenergic and serotonin receptors, which may contribute to the antidepressant activity.



Pregabaline: Pregabalin is a 3-isobutyl derivative of gamma-amino butyric acid (GABA) with anti-convulsant, anti-epileptic, anxiolytic, and analgesic activities. Although the exact mechanism of action is unknown, pregabalin selectively binds to alpha2delta (A2D) subunits of presynaptic voltage-dependent calcium channels (VDCCs) located in the central nervous system (CNS). Binding of pregabalin to VDCC A2D subunits prevents calcium influx and the subsequent calcium-dependent release of various neurotransmitters, including glutamate, norepinephrine, serotonin, dopamine, and substance P, from the presynaptic nerve terminals of hyperexcited neurons; synaptic transmission is inhibited and neuronal excitability is diminished. Pregabalin does not bind directly to GABA-A or GABA-B receptors and does not alter GABA uptake or degradation.

8. Pharmaceutical particulars

8.1 Incompatibilities

None.

8.2 Shelf-life

4 Years from the date of manufacture

8.3 Packaging information

AmNuring P is available as pack of 10 tablets.

8.4 Storage and handling instructions

Store below 25^0C and in dry place. Protect from light. Keep away from children.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

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

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

9.8 Contraindications

Refer part 4.3

10. Manufactured by THE MADRAS PHARMACEUTICALS

11. Details of permission or license number with date

LIC NO.110 , 13.11.1989

12. Date of revision: January 2022