

# AmNurite P<sup>®</sup> Tablets

**Each Tablet Contains**

Amitryptiline – 10 mg

Pregabalin – 75 mg

## PHARMACEUTICAL INFORMATION –

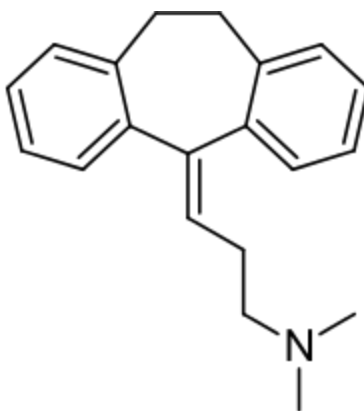
### Amitryptiline

**Generic name:** Amitryptiline

**Chemical name:** 3-(10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-N,N-dimethylpropan-1-amine

**Molecular mass:** 277.403 g/mol

**Structural formula:**



**Empirical formula –** C<sub>20</sub>H<sub>23</sub>N

**Storage and Stability:**

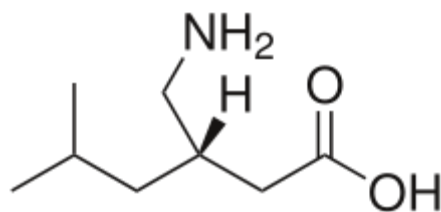
### Pregabalin

**Generic name:** Pregabalin

**Chemical name:** (S)-3-(aminomethyl)-5-methylhexanoic acid

**Molecular mass:** 277.403 g/mol

**Structural formula:**



**Empirical formula** – C<sub>8</sub>H<sub>17</sub>NO<sub>2</sub>

## **PHARMACOKINETIC PROPERTIES –**

### **Amitriptyline**

Amitriptyline is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring between 2 and 12 hours after administration. Bioavailability of the drug is between 30 and 60% due to extensive first pass metabolism of the drug in the liver. Amitriptyline is demethylated in the liver to its primary active metabolite, nortriptyline.

Amitriptyline is over 90% protein bound. Its elimination half-life varies from 10 to 50 hours, with an average of 15 hours. Within 24 hours, approximately 25 to 50% of a dose of amitriptyline is excreted in the urine as inactive metabolites; small amounts are excreted in the bile.

Routine serum drug concentration monitoring is not warranted but may be useful to assess compliance or suspected toxicity. Recommended therapeutic trough levels, i.e., the sum of both amitriptyline and its metabolite nortriptyline, vary widely and range from 250 to 900 nmol/L (60 to 250 ng/mL). Ideally, the trough level should be taken 12 hours following administration of the last dose.

TCAs are thought to work by inhibiting reuptake of norepinephrine and serotonin in the CNS, which potentiates the neurotransmitters. They also have significant anticholinergics, antihistaminic, and alpha-adrenergic activity on the cardiac system. These classes of antidepressants also possess class 1A antiarrhythmic activity, which can lead to depression of cardiac conduction, potentially resulting in heart block or ventricular arrhythmias.

- **Metabolism:** Extensively by the liver within the CYP450: 1A2, 2D6 (primary), 3A4 substrate; active metabolites include nortriptyline.
- **Excretion:** Primarily in urine (18% unchanged), feces.
- **Half-life:** 10–26 hr (amitriptyline), 18–44 hr (nortriptyline).

**Pregabalin**

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  $\geq 90\%$  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 bioavailability.

**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. At clinical doses of 150 to 600 mg/day, the average steady-state plasma Pregabalin concentrations were approximately 1.5 and 6.0  $\mu\text{g/mL}$ , respectively.

**Metabolism**

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled 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. Renal clearance ( $CL_{cr}$ ) derived from Phase I studies was 73 mL/min. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see Special Populations, Renal Impairment).

**PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION –****Amitriptyline**

Amitriptyline has qualitatively similar pharmacologic actions to other tricyclic antidepressants in experimental animals. It is more sedative than imipramine, reducing spontaneous motor activity at lower doses. It also prolongs hexobarbital sleeping time, produces ataxia and has a disruptive effect on EEG activity and conditioned behaviour. Amitriptyline antagonizes or reverses the depressant effects of reserpine and tetrabenazine and potentiates the pressor effects of norepinephrine and various behavioural effects of amphetamine. It possesses anticholinergic, antihistaminic and weak antiserotonin action. Amitriptyline also decreases body

temperature, lowers blood pressure in the anesthetized dog and has a quinidine-like effect on the heart.

Amitriptyline is absorbed slowly from the gastrointestinal tract in experimental animals. The drug is distributed in liver, lung, and brain tissue. Amitriptyline is detoxified in the liver where it undergoes N-demethylation to nortriptyline, which is further demethylated. Amitriptyline is excreted in the urine and bile as conjugates of the cis and trans isomers of 10-hydroxynortriptyline.

### **Amitriptyline -**

Its antidepressant effect 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-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub> & 5-HT<sub>7</sub>
- Inhibition of Nicotinic Acetylcholine Receptors

### **Pregabalin**

In vitro studies show that pregabalin binds to an auxiliary subunit ( $\alpha 2\text{-}\delta$  protein) of voltage-gated calcium channels in the central nervous system, potentially displacing [3H]-gabapentin. Two lines of evidence indicate that binding of pregabalin to the  $\alpha 2\text{-}\delta$  site is required for analgesic and anticonvulsant activity in animal models: (1) Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and (2) Studies of pregabalin in mutant mice with defective drug binding to the  $\alpha 2\text{-}\delta$  protein. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

Pregabalin does not show affinity for receptor sites or alter responses associated with the action of several common drugs for treating seizures or pain.

Pregabalin does not interact with either GABA<sub>A</sub> or GABA<sub>B</sub> receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of acute GABA uptake or degradation. Pregabalin prevents pain-related behaviours in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia. Pregabalin also shows efficacy in animal models of seizures, including maximal electroshock tonic extensor seizures in mice or rats, threshold clonic seizures from pentylenetetrazol, behavioural and electrographic seizures in hippocampal kindled rats, and tonic and clonic seizures in DBA/2 audiogenic mice. Pregabalin does not reduce the incidence of spontaneous absence seizures in Genetic Absence Epilepsy in Rats from Strasbourg (GAERS).

## **INDICATION –**

Painful Neuropathies

- Neuritis
- In painful diabetic neuropathy
- Spondylitis
- Chronic Low Back Pain
- Radiculopathy
- Trigeminal Neuralgia
- Post herpetic neuralgia
- Can be prescribed in diabetic patients on Pioglitazone

## **CONTRAINDICATIONS –**

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

## **DOSAGE AND ADMINISTRATION –**

1 Tablet O.D

## **ADVERSE EFFECTS –**

### **Amitryptiline**

**Behavioral:** drowsiness, fatigue, activation of latent schizophrenia, disorientation, confusional states, hallucinations, delusions, hypomanic reactions, disturbed concentration, nightmares, insomnia, restlessness, agitation, excitement, jitteriness, anxiety, giddiness.

**Neurological:** epileptiform seizures, coma, dizziness, tremors, numbness, tingling, parasthesias of the extremities, peripheral neuropathy, headache, ataxia, alteration in EEG patterns, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus, incoordination, and slurred speech.

**Anticholinergic:** urinary retention, dilatation of the urinary tract, constipation, paralytic ileus, especially in the elderly, hyperpyrexia, dry mouth, blurred vision, disturbance of accommodation, increased intraocular pressure, precipitation of latent glaucoma, aggravation of existing glaucoma, and mydriasis.

**Cardiovascular:** quinidine-like effect and other non-specific ECG changes and changes in AV conduction, prolonged conduction time, asystole, hypotension, syncope, hypertension, palpitation, arrhythmias, heart block, ventricular tachycardia, fibrillation, myocardial infarction, stroke, unexpected death in patients with cardiovascular disorders.

**Hematologic:** bone marrow depression, including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia.

**Allergic:** skin rash, urticaria, photosensitization, edema of the face and tongue, itching.

**Gastrointestinal:** nausea, epigastric distress, heartburn, vomiting, hepatitis (including altered liver function and jaundice), anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue may occur.

**Endocrine:** testicular swelling, gynecomastia and impotence in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, elevation and lowering of blood sugar levels, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

**Miscellaneous:** weakness, increased perspiration, edema, urinary frequency, alopecia, increased appetite, weight gain, weight loss.

Withdrawal Symptoms: Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within 2 weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance. These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants.

## **OVERDOSAGE**

### **Amitriptyline**

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 polyradiculoneuropathy; 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 overdose 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 life-threatening 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 CNS-depressant action.

Dialysis is of no value in amitriptyline overdose because of the low plasma concentrations of amitriptyline. Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdose 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.

### **WARNINGS**

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 those receiving thyroid medication.

### **PRECAUTIONS**

#### **Amitriptyline**

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.

## **Pregabalin**

### **Hereditary Problems of Galactose Metabolism**

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### **Weight Gain**

In the controlled studies, weight gain occurred more frequently in patients treated with LYRICA than in patients treated with placebo. LYRICA associated weight gain was related to dose and length of exposure, but did not appear to be associated with baseline BMI, gender or age.

In accordance with current clinical practice, some diabetic patients who gain weight on LYRICA treatment may need to adjust hypoglycaemic medications.

### **Hypersensitivity Reactions**

There have been reports in the post-marketing experience of hypersensitivity reactions, including cases of angioedema. LYRICA should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

### **Dizziness and Somnolence**

LYRICA causes dizziness and somnolence (see ADVERSE EFFECTS). In the controlled studies, dizziness and somnolence generally began shortly after initiation of LYRICA and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46%.

There have also been reports of loss of consciousness, confusion, and mental impairment.

### **Suicidal Behaviour and Ideation**

Antiepileptic drugs (AED), including LYRICA, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.



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

Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

## **DRUG INTERACTIONS –**

### **Amitriptyline**

- 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 anesthetics, close supervision and careful adjustment of dosage are required. Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.
- 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 to 150 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, aminosalicic acid, H<sub>2</sub>-blockers and colchicine.

## **SPECIAL POPULATIONS**

### **Pregnant Women:**

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 is 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.

### **Pediatrics:**

Behavioural changes have been observed in children receiving tricyclics for the treatment of enuresis.

**Geriatrics:**

Elderly patients are particularly liable to experience adverse reactions: especially agitation, confusion and postural hypotension.

In general, lower doses are recommended for elderly patients which 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.

**SHELF-LIFE -**

**PACKAGING INFORMATION -**