Amnurite® Tablets

Each Tablet Contains

- **Amitriptyline – 10 / 25 mg**
- **Mecobalamin – 1500 mcg SR**

PHARMACEUTICAL INFORMATION –

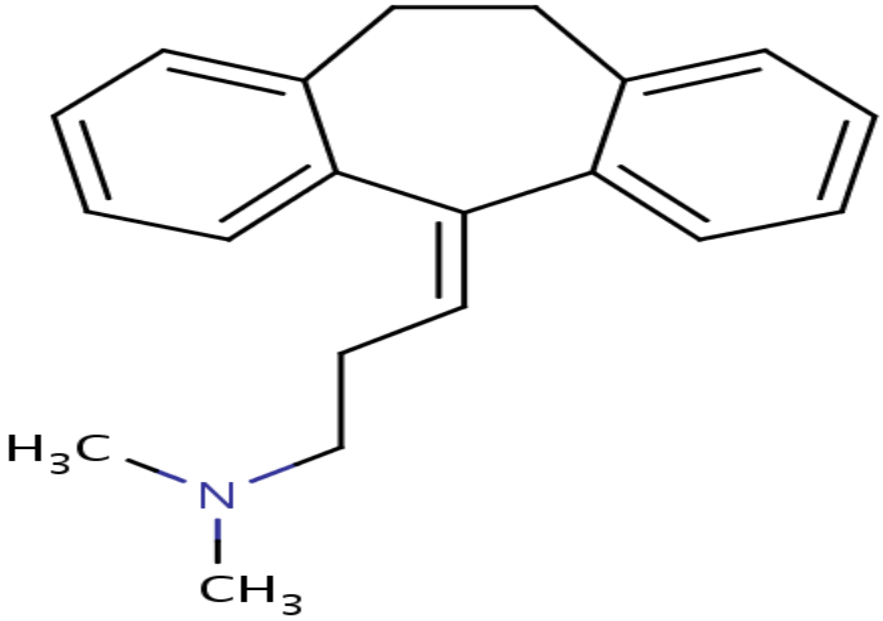
AMITRIPTYLINE

Generic name: Amitriptyline

Chemical name: 3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-N,N-dimethyl propan - 1 - amine

Molecular mass: 277.403 g/mol

Structural formula:



Empirical formula – C20 H23 N

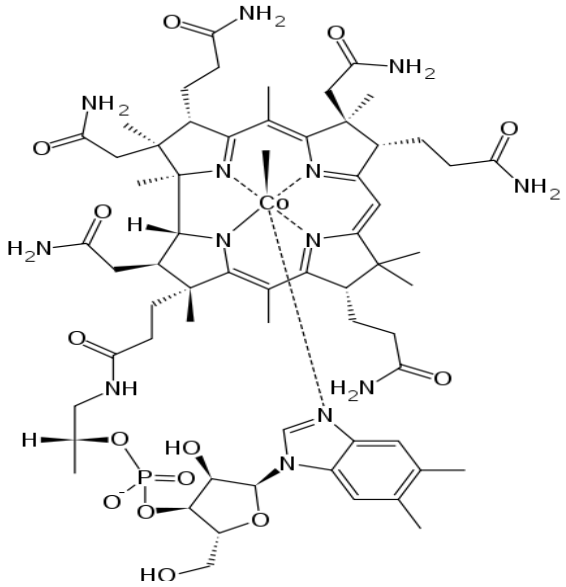
Storage and Stability: Store at room temperature (15°to 30°C)

MECOBALAMIN

Generic name: Methylcobalamin

Molecular mass: 1344.40 g/mol

Structural formula:



Empirical formula – C63H91CoN13O14P

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).

Mecobalamin

Evidence indicates Methylcobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B12. Experiments have demonstrated similar absorption of methylcobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin. Human urinary excretion of methylcobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention.

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION –

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.

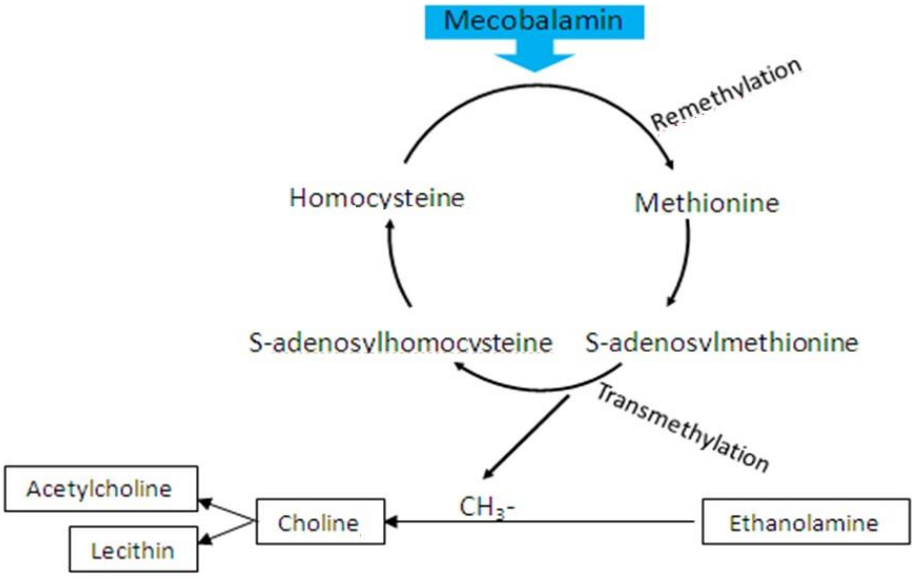
Amitriptyline -

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_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6 & 5-HT_7
- Inhibition of Nicotinic Acetylcholine Receptors

Mecobalamin -

- Enhances synthesis proteins in nerve cells
  - promotes myelinization
  - axonal regeneration
- Helps in generation of enzyme methionine synthase - regeneration of methionine from homocysteine.
- Restores diminished neurotransmitter (Acetylcholine) levels.



INDICATION –

Painful Neuropathy

- Neuritis
- Diabetic Neuropathy
- Spondylitis
- Chronic Low Back Pain
- Radiculopathy

- Trigeminal neuralgia
- Post Herpetic Neuralgia

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 taken 24 hourly i.e. OD.

ADVERSE EFFECTS –

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.

As Mecobalamin is a water soluble vitamin, it does not accumulate in the body causing toxicity,

OVERDOSAGE

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 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 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.

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

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.

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 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 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.

Reduced serum concentrations with oral contraceptives.

Reduced effects in anaemia with parenteral chloramphenicol.

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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 -

24 Months

PACKAGING INFORMATION -

Available in blister pack of 10 Tablets.