

PRODUCT MONOGRAPH

ELAVIL®

Amitriptyline Hydrochloride Tablets USP

10, 25, 50 and 75 mg

Antidepressant

**AA PHARMA INC.
1165 Creditstone Road, Unit #1
Vaughan, ON
L4K 4N7**

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THERAPEUTIC CLASSIFICATION

Antidepressant

ACTIONS AND CLINICAL PHARMACOLOGY

Amitriptyline hydrochloride is a tricyclic antidepressant with sedative properties. Its mechanism of action in man is not known. Amitriptyline inhibits the membrane pump mechanism responsible for the re-uptake of transmitter amines, such as norepinephrine and serotonin, thereby increasing their concentration at the synaptic clefts of the brain. Amitriptyline has pronounced anticholinergic properties and produces EKG changes and quinidine-like effects on the heart (See ADVERSE REACTIONS). It also lowers the convulsive threshold and causes alterations in EEG and sleep patterns.

Orally administered amitriptyline is readily absorbed and rapidly metabolized. Steady-state plasma concentrations vary widely and this variation may be genetically determined.

Amitriptyline is primarily excreted in the urine, mostly in the form of metabolites, with some excretion also occurring in the feces.

INDICATIONS AND CLINICAL USE

ELAVIL® (amitriptyline hydrochloride) is indicated in the drug management of depressive illness.

ELAVIL® may be used in depressive illness of psychotic or endogenous nature and in selected patients with neurotic depression. Endogenous depression is more likely to be alleviated than are other depressive states. ELAVIL®, because of its sedative action, is also of value in alleviating the anxiety component of depression.

As with other tricyclic antidepressants, ELAVIL® may precipitate hypomanic episodes in patients with bipolar depression. These drugs are not indicated in mild depressive states and depressive reactions.

CONTRAINDICATIONS

In patients who have shown prior hypersensitivity to it. It should not be given concomitantly with a MAO inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and MAO inhibiting drugs simultaneously. When it is desired to substitute ELAVIL® (amitriptyline hydrochloride) for a MAO inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. ELAVIL® should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

This drug is not recommended for use during the acute recovery phase following myocardial infarction and in the presence of acute congestive heart failure.

See Pregnancy under Warnings.

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.

Concurrent administration of amitriptyline and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Close supervision is required when amitriptyline is given to hyperthyroid patients or those receiving thyroid medication.

Occupational Hazards: May impair mental and/or physical abilities required for performance

of hazardous tasks, such as operating machinery or driving a motor vehicle.

Pregnancy: There are no well-controlled studies in pregnant women; therefore, in administering the drug to pregnant patients or women who may become pregnant, the potential benefits must be weighed against the possible hazards to mother and child.

Lactation: Amitriptyline is detectable in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, a decision should be made whether to discontinue nursing or discontinue the drug.

Children: In view of the lack of experience with the use of this drug in the treatment of depression in children, amitriptyline is not recommended for depressed patients under 12 years of age.

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.

When amitriptyline is used to treat the depressive component of schizophrenia, activation or aggravation of existing psychotic manifestation may occur. Likewise, manic depressive patients

may experience hypomanic or manic episodes and hyperactive or agitated patients may become overstimulated. Paranoid delusions, with or without associated hostility, may be exaggerated. A reduction in dose or discontinuation of amitriptyline may be indicated and administration of a neuroleptic such as a phenothiazine, be considered under these circumstances.

Seriously depressed patients should be carefully supervised. The possibility of suicide in depressed patients remains during treatment. Patients should not have access to large quantities of this drug during treatment.

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 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.

ADVERSE REACTIONS

Note: Included in the listing which follows are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

SYMPTOMS

High doses may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Overdosage may cause drowsiness, hypothermia, tachycardia and other arrhythmic abnormalities, such as bundle branch block, ECG evidence of impaired conduction, congestive heart failure, disorders of ocular motility, convulsions, severe hypotension, stupor, coma, polyradiculoneuropathy and constipation. Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under Adverse Effects.

In patients with glaucoma, even average doses may precipitate an attack.

TREATMENT

Treatment is symptomatic and supportive. Cardiac arrhythmias and CNS involvement pose the greatest threat and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdose of amitriptyline, particularly children, should be hospitalized and kept under close surveillance. Induced emesis and gastric lavage are recommended in the alert and conscious patient. Following gastric lavage, activated charcoal may be administered. Twenty to 30 g of activated charcoal may be given every 4 to 6 hours during the first 24 to 48 hours after ingestion. It may be helpful to leave the tube in the stomach, with irrigation (with an electrolyte balanced fluid) and continual aspiration of stomach contents

possibly promoting more rapid elimination of the drug from the body. If the patient is not alert, a cuffed endotracheal tube should be inserted before lavage is performed, and emesis should not be induced. An open airway should be maintained. Standard measures (oxygen, i.v. fluids, corticosteroids) may be used to manage circulatory shock and metabolic acidosis. Norepinephrine or other pressor agents (but no epinephrine) by i.v. drop infusion under continuous monitoring may be used if necessary. Failing respiration must be maintained by artificial means, but respiratory stimulants should not be used. Regulate body temperature. Hyperpyrexia should be controlled by external measures, such as ice packs and cooling sponge baths. Catheterization should be performed in the unconscious patient. Continuous cardiac monitoring should be instituted in all patients, particularly in the presence of ECG abnormalities and should be maintained for several days after the cardiac rhythm has returned to normal. Because of its effects on cardiac conduction, digitalis should be used only with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

It has been reported that i.v. administration of physostigmine salicylate may reverse some of the CNS and cardiovascular effects of tricyclic antidepressants. The dosage that has been recommended for adults is 1 to 2 mg in **very slow** i.v. injection. In children, the initial dosage should not exceed 0.5 mg and should be adjusted to age and response. Since physostigmine has a short duration of action, administration may have to be repeated at 30 to 60 minute intervals particularly in life-threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dose of physostigmine. Because physostigmine itself may be toxic, it is not recommended for routine use.

The room should be darkened, with a minimal amount of external stimulation, to reduce the tendency to convulsions. If convulsions occur, they should preferably be controlled by non-barbiturate sedatives, such as chlordiazepoxide or diazepam, or by an inhalation anesthetic (amitriptyline increases the CNS depressant but not the anticonvulsant action of barbiturates). Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered. Dialysis has not been found to be of value for intoxication by amitriptyline alone due to low plasma concentrations of the drug.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Outpatient Adults: The recommended initial dose for ambulatory patients is 25 mg 3 times a day.

Depending upon tolerance and response, this may be increased to a total of 150 mg a day.

Increases are made preferably in the late afternoon and/or bedtime doses. The sedative effect is usually rapidly apparent. The antidepressant activity may be evident within 3 or 4 days or may take up to 30 days to develop adequately.

Hospitalized Patients: Severely ill or hospitalized patients may require 100 mg a day initially.

This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

Adolescent and Elderly Patients: In general, lower dosages are recommended for these patients.

In those patients who may not tolerate higher doses, 50 mg daily may be satisfactory. The dose may be administered in divided doses or as a single dose preferably in the evening or at bedtime.

Maintenance: When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. The usual maintenance dose is 50 to 100 mg/day in divided doses; however, in suitable patients, the total daily dosage may be given in a single dose, preferably at bedtime. It is appropriate to continue maintenance therapy throughout the active phase of the depression and for the expected duration of the depressive episode, in order to lessen the possibility of relapse.

Plasma Levels: Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or non-compliance is suspected. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.

PHARMACEUTICAL INFORMATION**DRUG SUBSTANCE**

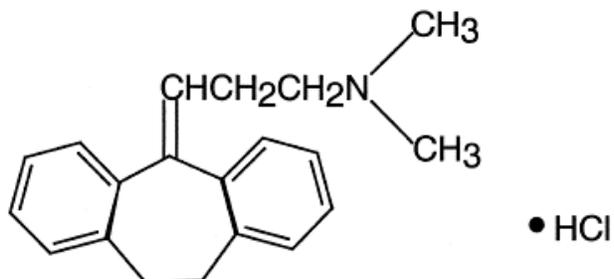
Proper/Common Name: Amitriptyline Hydrochloride

Chemical Name: 1-propanamine, 3-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-N,N-dimethyl-, hydrochloride

Molecular Formula: $C_{20}H_{23}N \cdot HCl$

Molecular Weight: 313.86

Structural Formula:



Description: Amitriptyline hydrochloride is a white or practically white, odorless or practically odorless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methanol; insoluble in ether.

- Composition: In addition to amitriptyline hydrochloride, each tablet contains the non- medicinal ingredients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and carnauba wax.
- ELAVIL® 10 mg: In addition to the ingredients listed under composition, the ELAVIL® 10 mg tablet contains the dye Brilliant Blue FCF AL Lake 12%.
- ELAVIL® 25 mg: In addition to the ingredients listed under composition, the ELAVIL® 25 mg tablet contains the dye D & C Yellow #10 AL 14-18%.
- ELAVIL® 50 mg: In addition to the ingredients listed under composition, the ELAVIL® 50 mg tablet contains the dyes Sunset Yellow AL Lake 40% and Indigotine AL Lake 12-14% (Blue #2).
- ELAVIL® 75 mg: In addition to the ingredients listed under composition, the ELAVIL® 75 mg tablet contains the dye Sunset Yellow AL Lake 40%.

Stability and Storage Recommendations

Store at room temperature (15 - 30°C). Keep in a tightly closed container.

AVAILABILITY OF DOSAGE FORMS

ELAVIL® 10 mg: Each blue, round, biconvex, film coated tablet, engraved '10' on one side contains 10 mg of amitriptyline hydrochloride. Available in bottles of 100 and 1000, unit dose packages of 100 (10 x 10) tablets.

ELAVIL® 25 mg: Each yellow, round, biconvex, film coated tablet, engraved '25' on one side contains 25 mg of amitriptyline hydrochloride. Available in bottles of 100, 1000 and 3000, unit dose packages of 100 (10 x 10) tablets.

ELAVIL® 50 mg: Each brown, round, biconvex, film coated tablet, engraved '50' on one side contains 50 mg of amitriptyline hydrochloride. Available in bottles of 100 and 1000, unit dose packages of 100 (10 x 10) tablets.

ELAVIL® 75 mg: Each orange, round, biconvex, film coated tablet, engraved '75' on one side contains 75 mg of amitriptyline hydrochloride. Available in bottles of 100 tablets.

PHARMACOLOGY

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.

TOXICOLOGY

ACUTE:

| SPECIES | ROUTE | SEX | LD ₅₀ (mg of base/kg) | 95% FUDUCIAL LIMITS |
|---------|-------|-----|-------------------------------------|------------------------|
| Mice | PO | F | 289 | (249 – 335) |
| | IP | F | 76 | (71 – 81) |
| | SO | F | 328 | (279 – 386) |
| Rats | PO | F | 464 | (370 – 583) |
| | PO | M | 600 | (403 – 872) |
| | IP | F | 67 | (59 – 76) |
| | IP | M | 77 | (67 – 88) |
| | SC | F | 1350 | (1130 – 1162) |
| | SC | M | 1235 | (1010 – 1510) |

Signs of toxicity included sedation, ataxia, ptosis, lacrimation, decreased respiratory rate, partial loss of righting reflex and convulsions.

SUBACUTE AND CHRONIC

Dogs: Oral doses of 20 and 40 mg/kg/day were tolerated for 6 months without hematologic, biochemical or anatomical evidence of drug toxicity. Signs of drug effect included slight to

marked sedation, a slight tachycardia, slight ataxia, and occasionally, excessive salivation and emesis. Oral doses of 80 mg/kg/day in a 6 month study were not well tolerated: 2 of 4 dogs died within 3 weeks after exhibiting severe ataxia and sedation. No other drug-related effects were observed. Doses of 100 mg/kg/day or greater were not tolerated for more than a few days. The only effect observed was a small amount of fat in the periportal region of the liver without evidence of necrosis.

Rats: 0, 15, 30 or 60 mg/kg/day were given orally by gavage, 5 days a week, for periods up to 48 weeks. Doses of 60 mg/kg/day produced a moderate depression of body weight and a slight increase in liver weight.