F.P.O.

PACKAGE INSERT

64201-01

Elavil®

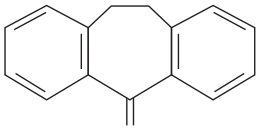
amitriptyline HCl

Tablets and Injection

Rev 02/03

DESCRIPTION

Amitriptyline HCl is 3-(10,11-dihydro-5*H*-dibenzo [a,*d*] cycloheptene-5-ylidene)-*N*,*N*-dimethyl-1-propanamine hydrochloride. Its empirical formula is $C_{20}H_{23}N \cdot HCl$ and its structural formula is:



• HCl

$CHCH_2CH_2N(CH_3)_2$

Amitriptyline HCl, a dibenzocycloheptadiene derivative, has a molecular weight of 313.87. It is a white, odorless, crystalline compound which is freely soluble in water.

ELAVIL* (Amitriptyline HCl) is supplied as 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg tablets and as a sterile solution for intramuscular use. Inactive ingredients of the tablets are calcium phosphate, cellulose, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, stearic acid, talc, and titanium dioxide. Tablets ELAVIL 10 mg also contain FD&C Blue 1. Tablets ELAVIL 25 mg also contain D&C Yellow 10, FD&C Blue 1, and FD&C Yellow 6. Tablets ELAVIL 50 mg also contain D&C Yellow 10, FD&C Yellow 6 and iron oxide. Tablets ELAVIL 75 mg also contain FD&C Yellow 6. Tablets ELAVIL 100 mg also contain FD&C Blue 2 and FD&C Red 40. Tablets ELAVIL 150 mg also contain FD&C Blue 2 and FD&C Yellow 6. Each milliliter of the sterile solution contains:

Amitriptyline hydrochloride . . . . .10 mg
Dextrose . . . . . .44 mg
Water for Injection, q.s. . . . . .1 mL

Added as preservatives:
Methylparaben . . . . . .1.5 mg
Propylparaben . . . . . .0.2 mg

ACTIONS

ELAVIL is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

INDICATIONS

For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

ELAVIL is contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to replace a monoamine oxidase inhibitor with ELAVIL, a minimum of 14 days should be allowed to elapse after the former is discontinued. ELAVIL should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

ELAVIL should not be given concurrently with Cisapride due to the potential for increased QT interval and increased risk for arrhythmia.

This drug is not recommended for use during the acute recovery phase following myocardial infarction.

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ELAVIL should not be given concurrently with Cisapride due to the potential for increased QT interval and increased risk for arrhythmia.

This drug is not recommended for use during the acute recovery phase following myocardial infarction.

WARNINGS

ELAVIL may block the antihypertensive action of guanethidine or similarly acting compounds.

It should be used with caution in patients with a history of seizures and, because of its atropine-like action, in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. In patients with angle-closure glaucoma, even average doses may precipitate an attack.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including ELAVIL, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class.

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

ELAVIL may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Usage in Pregnancy: Pregnancy Category C: Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2 to 40 mg/kg/day (up to 13 times the maximum recommended human dose**). Studies in literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28 to 100 mg/kg/day (9 to 33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of fetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of the cranial bones.

Amitriptyline has been shown to cross the placenta. Although a causal relationship has not been established, there have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy.

There are no adequate and well-controlled studies in pregnant women. ELAVIL should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: Amitriptyline is excreted into breast milk. In one report in which a patient received amitriptyline 100 mg/day while nursing her infant, levels of 83-141 ng/mL were detected in the mother's serum. Levels of 135-151 ng/mL were found in the breast milk, but no trace of the drug could be detected in the infant's serum.

Because of the potential for serious adverse reactions in nursing infants from amitriptyline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Usage in Pediatric Patients: In view of the lack of experience with the use of this drug in pediatric patients, it is not recommended at the present time for patients under 12 years of age.

PRECAUTIONS

Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. In these circumstances the dose of amitriptyline may be reduced or a major tranquilizer such as perphenazine may be administered concurrently.

The possibility of suicide in depressed patients remains until significant remission occurs. Potentially suicidal patients should not have access to large quantities of this drug. Prescriptions should be written for the smallest amount feasible.

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

When possible, the drug should be discontinued several days before elective surgery.

Both elevation and lowering of blood sugar levels have been reported.

ELAVIL should be used with caution in patients with impaired liver function.

Drug Interactions: Drugs Metabolized by P450 2D6 – The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the

of TCA may become abnormally toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Monoamine oxidase inhibitors - see CONTRAINDICATIONS section. Guanethidine or similarly acting compounds; thyroid medication; alcohol, barbiturates and other CNS depressants; and disulfiram - see WARNINGS section.

When ELAVIL is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when ELAVIL is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with one gram of ethchlorvynol and 75 - 150 mg of ELAVIL.

Information for Patients: While on therapy with ELAVIL, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Geriatric Use: Clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic function, concomitant disease and other drug therapy in elderly patients.

Geriatric patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants including ELAVIL. Peripheral anticholinergic effects include tachycardia, urinary retention, constipation, dry mouth, blurred vision, and exacerbation of narrow-angle glaucoma. Central nervous system anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation, and delirium. Elderly patients taking ELAVIL may be at increased risk for falls. Elderly patients should be started on low doses of ELAVIL and observed closely (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing 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.

Cardiovascular: Myocardial infarction; stroke; nonspecific ECG changes and changes in AV conduction; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; syncope; hypertension; tachycardia; palpitation.

CNS and Neuromuscular: Coma; seizures; hallucinations; delusions; confusional states; disorientation; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of the extremities; extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia; dysarthria; disturbed concentration; excitement; anxiety; insomnia; restlessness; nightmares; drowsiness; dizziness; weakness; fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention; dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased ocular pressure, mydriasis; dry mouth.

Allergic: Skin rash; urticaria; photosensitization; edema of face and tongue.

Hematologic: Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura; eosinophilia.

(CONTINUED ON REVERSE SIDE)

Hematologic: Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura; eosinophilia.

(CONTINUED ON REVERSE SIDE)

Gastrointestinal: Rarely hepatitis (including altered liver function and jaundice); nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; impotence; elevation and lowering of blood sugar levels.

Other: Alopecia; edema; weight gain or loss; urinary frequency; increased perspiration.

Withdrawal Symptoms: After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within two 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 2-7 days following cessation of chronic therapy with tricyclic antidepressants.

Causal Relationship Unknown: Other reactions, reported under circumstances where a causal relationship could not be established, are listed to serve as alerting information to physicians:

Body as a Whole: Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

Digestive: Hepatic failure, ageusia.

Postmarketing Adverse Events: A syndrome resembling neuroleptic malignant syndrome (NMS) has been very rarely reported after starting or increasing the dose of ELAVIL, with and without concomitant medications known to cause NMS. Symptoms have included muscle rigidity, fever, mental status changes, diaphoresis, tachycardia, and tremor.

Very rare cases of serotonin syndrome (SS) have been reported with ELAVIL in combination with other drugs that have a recognized association with SS.

Very rare cases of cardiomyopathy have been reported with ELAVIL.

DOSAGE AND ADMINISTRATION

Oral Dosage

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

Initial Dosage for Adults: For outpatients 75 mg of amitriptyline HCl a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg per day. Increases are made preferably in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.

An alternate method of initiating therapy in outpatients is to begin with 50 to 100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg per day.

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. Ten milligrams 3 times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages.

Maintenance: The usual maintenance dosage of amitriptyline HCl is 50 to 100 mg per day. In some patients 40 mg per day is sufficient. For maintenance therapy the total daily dosage may be given in a single dose preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

Intramuscular Dosage

Initially, 20 to 30 mg (2 to 3 mL) four times a day.

When ELAVIL Injection is administered intramuscularly, the effects may appear more rapidly than with oral administration.

When ELAVIL Injection is used for initial therapy in patients unable or unwilling to take ELAVIL Tablets, the tablets should replace the injection as soon as possible.

Usage in Pediatric Patients

In view of the lack of experience with the use of this drug in pediatric patients, it is not recommended at the present time for patients under 12 years of age.

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 noncompliance is suspected. Because of increased intestinal transit time and decreased hepatic metabolism in elderly patients, plasma levels are generally higher for a given oral dose of ELAVIL than in younger patients. Elderly patients should be monitored carefully and quantitative serum levels obtained as clinically appropriate. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.***

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is

not on the basis of plasma levels.***

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Manifestations: Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. In addition, a rightward axis shift in the terminal QRS complex together with a prolonged QT interval and sinus tachycardia are specific and sensitive indicators of first generation tricyclic overdose. The absence of these findings is not exclusionary. Prolonged PR interval, ST-T wave changes, ventricular tachycardia and fibrillation may also occur.

Other signs of overdose may include: impaired myocardial contractility, confusion, disturbed concentration, transient visual hallucinations, dilated pupils, disorders of ocular motility, agitation, hyperactive reflexes, polyradiculoneuropathy, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

Management:

General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during the period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. EMESIS IS CONTRAINDICATED.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO_2 <20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of pediatric and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

Tablets ELAVIL, 10 mg, are blue, round, film coated tablets, identified with "40" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0040-10 bottles of 100

Tablets ELAVIL, 25 mg, are yellow, round, film coated tablets, identified with "45" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0045-10 bottles of 100
NDC 0310-0045-50 bottles of 5000

Tablets ELAVIL, 50 mg, are beige, round, film coated tablets, identified with "41" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0041-10 bottles of 100

Tablets ELAVIL, 75 mg, are orange, round, film coated tablets, identified with "42" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0042-10 bottles of 100

Tablets ELAVIL, 100 mg, are mauve, round, film coated tablets, identified with "43" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0043-10 bottles of 100

Tablets ELAVIL, 150 mg, are blue, capsule shaped, film coated tablets, identified with "47" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0047-30 bottles of 30
NDC 0310-0047-10 bottles of 100

Injection ELAVIL, 10 mg/mL, is a clear, colorless

and "ELAVIL" on the other side. They are supplied as follows:

NDC 0310-0047-30 bottles of 30
NDC 0310-0047-10 bottles of 100

Injection ELAVIL, 10 mg/mL, is a clear, colorless solution, and is supplied as follows:

NDC 0310-0049-10 in 10 mL vials

Storage: Store Tablets ELAVIL in a well-closed container. Avoid storage at temperatures above 30°C (86°F). In addition, Tablets ELAVIL 10 mg must be protected from light and stored in a well-closed, light-resistant container.

Protect ELAVIL Injection from freezing and avoid storage above 30°C (86°F).

METABOLISM

Studies in man following oral administration of ^{14}C-labeled drug indicated that amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the drug was excreted within 24 hours.

Amitriptyline is metabolized by N-demethylation and bridge hydroxylation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

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Symposium on depression with special studies of a new antidepressant, amitriptyline. Dis Nerv Syst, (Sect 2) May 1961, pp 5-56.

* Registered trademark of AstraZeneca.

** Based on a maximum recommended amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50 kg patient.

*** Hollister LE: Monitoring Tricyclic Antidepressant Plasma Concentrations. JAMA 1979;241(23):2530-2533.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: MERCK & Co., Inc.
Whitehouse Station, NJ 08889, USA

64201-01
Rev 02/03

AstraZeneca

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Elavil®

amitriptyline HCl

Tablets and Injection

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DESCRIPTION

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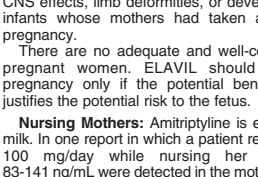

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Dextrose	44 mg
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Added as preservatives:	
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WARNINGS

ELAVIL may block the antihypertensive action of guanethidine or similarly acting compounds.

It should be used with caution in patients with a history of seizures and, because of its atropine-like action, in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. In patients with angle-closure glaucoma, even average doses may precipitate an attack.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including ELAVIL, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class.

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

ELAVIL may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Usage in Pregnancy: Pregnancy Category C: Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2 to 40 mg/kg/day (up to 13 times the maximum recommended human dose**). Studies in literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28 to 100 mg/kg/day (9 to 33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of fetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of the cranial bones.

Amitriptyline has been shown to cross the placenta. Although a causal relationship has not been established, there have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy.

There are no adequate and well-controlled studies in pregnant women. ELAVIL should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: Amitriptyline is excreted into breast milk. In one report in which a patient received amitriptyline 100 mg/day while nursing her infant, levels of 83-141 ng/mL were detected in the mother's serum. Levels of 135-151 ng/mL were found in the breast milk, but no trace of the drug could be detected in the infant's serum.

Because of the potential for serious adverse reactions in nursing infants from amitriptyline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Usage in Pediatric Patients: In view of the lack of experience with the use of this drug in pediatric patients, it is not recommended at the present time for patients under 12 years of age.

PRECAUTIONS

Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. In these circumstances the dose of amitriptyline may be reduced or a major tranquilizer such as perphenazine may be administered concurrently.

The possibility of suicide in depressed patients remains until significant remission occurs. Potentially suicidal patients should not have access to large quantities of this drug. Prescriptions should be written for the smallest amount feasible.

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

When possible, the drug should be discontinued several days before elective surgery.

Both elevation and lowering of blood sugar levels have been reported.

ELAVIL should be used with caution in patients with impaired liver function.

Drug Interactions: Drugs Metabolized by P450 2D6 – The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Monoamine oxidase inhibitors - see CONTRAINDICATIONS section. Guanethidine or similarly acting compounds; thyroid medication; alcohol, barbiturates and other CNS depressants; and disulfiram - see WARNINGS section.

When ELAVIL is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when ELAVIL is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with one gram of ethchlorvynol and 75 - 150 mg of ELAVIL.

Information for Patients: While on therapy with ELAVIL, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Geriatric Use: Clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic function, concomitant disease and other drug therapy in elderly patients.

Geriatric patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants including ELAVIL. Peripheral anticholinergic effects include tachycardia, urinary retention, constipation, dry mouth, blurred vision, and exacerbation of narrow-angle glaucoma. Central nervous system anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation, and delirium. Elderly patients taking ELAVIL may be at increased risk for falls. Elderly patients should be started on low doses of ELAVIL and observed closely (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing 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.

Cardiovascular: Myocardial infarction; stroke; nonspecific ECG changes and changes in AV conduction; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; syncope; hypertension; tachycardia; palpitation.

CNS and Neuromuscular: Coma; seizures; hallucinations; delusions; confusional states; disorientation; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of the extremities; extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia; dysarthria; disturbed concentration; excitement; anxiety; insomnia; restlessness; nightmares; drowsiness; dizziness; weakness; fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention; dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased ocular pressure, mydriasis; dry mouth.

Allergic: Skin rash; urticaria; photosensitization; edema of face and tongue.

Hematologic: Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura; eosinophilia.

(CONTINUED ON REVERSE SIDE)

Gastrointestinal: Rarely hepatitis (including altered liver function and jaundice); nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; impotence; elevation and lowering of blood sugar levels.

Other: Alopecia; edema; weight gain or loss; urinary frequency; increased perspiration.

Withdrawal Symptoms: After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within two 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 2-7 days following cessation of chronic therapy with tricyclic antidepressants.

Causal Relationship Unknown: Other reactions, reported under circumstances where a causal relationship could not be established, are listed to serve as alerting information to physicians:

Body as a Whole: Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

Digestive: Hepatic failure, ageusia.

Postmarketing Adverse Events: A syndrome resembling neuroleptic malignant syndrome (NMS) has been very rarely reported after starting or increasing the dose of ELAVIL, with and without concomitant medications known to cause NMS. Symptoms have included muscle rigidity, fever, mental status changes, diaphoresis, tachycardia, and tremor.

Very rare cases of serotonin syndrome (SS) have been reported with ELAVIL in combination with other drugs that have a recognized association with SS.

Very rare cases of cardiomyopathy have been reported with ELAVIL.

DOSAGE AND ADMINISTRATION

Oral Dosage

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

Initial Dosage for Adults: For outpatients 75 mg of amitriptyline HCl a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg per day. Increases are made preferably in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.

An alternate method of initiating therapy in outpatients is to begin with 50 to 100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg per day.

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. Ten milligrams 3 times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages.

Maintenance: The usual maintenance dosage of amitriptyline HCl is 50 to 100 mg per day. In some patients 40 mg per day is sufficient. For maintenance therapy the total daily dosage may be given in a single dose preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

Intramuscular Dosage

Initially, 20 to 30 mg (2 to 3 mL) four times a day.

When ELAVIL Injection is administered intramuscularly, the effects may appear more rapidly than with oral administration.

When ELAVIL Injection is used for initial therapy in patients unable or unwilling to take ELAVIL Tablets, the tablets should replace the injection as soon as possible.

Usage in Pediatric Patients

In view of the lack of experience with the use of this drug in pediatric patients, it is not recommended at the present time for patients under 12 years of age.

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 noncompliance is suspected. Because of increased intestinal transit time and decreased hepatic metabolism in elderly patients, plasma levels are generally higher for a given oral dose of ELAVIL than in younger patients. Elderly patients should be monitored carefully and quantitative serum levels obtained as clinically appropriate. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.***

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Manifestations: Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. In addition, a rightward axis shift in the terminal QRS complex together with a prolonged QT interval and sinus tachycardia are specific and sensitive indicators of first generation tricyclic overdose. The absence of these findings is not exclusionary. Prolonged PR interval, ST-T wave changes, ventricular tachycardia and fibrillation may also occur.

Other signs of overdose may include: impaired myocardial contractility, confusion, disturbed concentration, transient visual hallucinations, dilated pupils, disorders of ocular motility, agitation, hyperactive reflexes, polyradiculoneuropathy, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

Management:

General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during the period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. EMESIS IS CONTRAINDICATED.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO_2 <20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of pediatric and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

Tablets ELAVIL, 10 mg, are blue, round, film coated tablets, identified with "40" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0040-10 bottles of 100

Tablets ELAVIL, 25 mg, are yellow, round, film coated tablets, identified with "45" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0045-10 bottles of 100
NDC 0310-0045-50 bottles of 5000

Tablets ELAVIL, 50 mg, are beige, round, film coated tablets, identified with "41" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0041-10 bottles of 100

Tablets ELAVIL, 75 mg, are orange, round, film coated tablets, identified with "42" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0042-10 bottles of 100

Tablets ELAVIL, 100 mg, are mauve, round, film coated tablets, identified with "43" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0043-10 bottles of 100

Tablets ELAVIL, 150 mg, are blue, capsule shaped, film coated tablets, identified with "47" debossed on one side and "ELAVIL" on the other side. They are supplied as follows:
NDC 0310-0047-30 bottles of 30
NDC 0310-0047-10 bottles of 100

Injection ELAVIL, 10 mg/mL, is a clear, colorless solution, and is supplied as follows:
NDC 0310-0049-10 in 10 mL vials

Storage: Store Tablets ELAVIL in a well-closed container. Avoid storage at temperatures above 30°C (86°F). In addition, Tablets ELAVIL 10 mg must be protected from light and stored in a well-closed, light-resistant container.

Protect ELAVIL Injection from freezing and avoid storage above 30°C (86°F).

METABOLISM

Studies in man following oral administration of ^{14}C-labeled drug indicated that amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the drug was excreted within 24 hours.

Amitriptyline is metabolized by N-demethylation and bridge hydroxylation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

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* Registered trademark of AstraZeneca.
** Based on a maximum recommended amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50 kg patient.
*** Hollister LE: Monitoring Tricyclic Antidepressant Plasma Concentrations. JAMA 1979;241(23):2530-2533.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: MERCK & Co., Inc.
Whitehouse Station, NJ 08889, USA

64201-01
Rev 02/03

AstraZeneca

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