

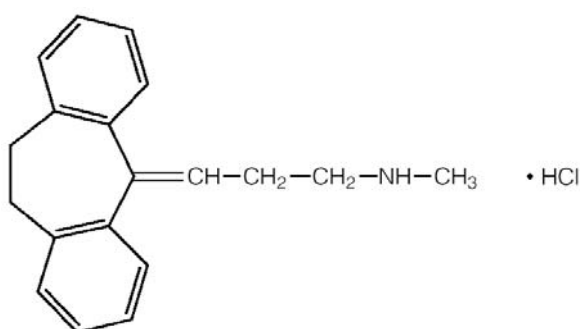
ALLEGRON®

(nortriptyline hydrochloride)

DESCRIPTION

ALLEGRON (nortriptyline hydrochloride) is a 5-(3-methylamino-propylidene)- 10,11-dihydro-5H-dibenzo [a,d] cycloheptene hydrochloride. Its molecular weight is 299.8 and its empirical formula is C₁₉H₂₁N.HCl.

The structural formula is as follows:



ALLEGRON 10 mg and 25 mg tablets contain 10 mg and 25 mg nortriptyline (present as the hydrochloride) as the active ingredient, respectively. Excipients include maize starch, magnesium stearate, lactose, calcium phosphate, glycerol and hypromellose. ALLEGRON 25 mg tablets also contain sunset yellow FCF aluminium lake as the colouring agent.

ACTIONS

The mechanism of mood elevation by such tricyclic antidepressants is at present unknown. ALLEGRON is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine and acetylcholine. It increases the pressor effect of noradrenaline but blocks the pressor effect of phenethylamine. Studies suggest that ALLEGRON interferes with the transport, release and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that ALLEGRON has a combination of stimulant and depressant properties.

INDICATIONS

ALLEGRON is indicated for the treatment of major depression.

CONTRAINDICATIONS

The use of ALLEGRON or other tricyclic antidepressants concurrently with a monoamine oxidase (MAO) inhibitor is contraindicated. Hyperpyretic crises, severe convulsions and fatalities have occurred when similar tricyclic antidepressants were used in such

combinations. It is advisable to have discontinued the MAO inhibitor for at least two weeks before treatment with ALLEGRON is started.

Patients hypersensitive to ALLEGRON should not be given the drug.

Cross sensitivity between ALLEGRON and other dibenzazepines is a possibility. ALLEGRON is contraindicated during the acute recovery period after myocardial infarction.

PRECAUTIONS

Clinical Worsening and Suicide Risk Associated with Psychiatric Disorders

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and other) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the

pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Pooled analysis of short term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months). Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder and for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for ALLEGON should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Patients with cardiovascular disease should be given ALLEGON only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, ALLEGON should be used with great caution in patients with glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when ALLEGON is administered, since this drug is known to lower the convulsive threshold.

Great care is required if ALLEGON is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Impairment of Motor Co-ordination - ALLEGON may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly.

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicide attempts or

overdosage, especially in patients with histories of emotional disturbances or suicidal ideation. The patient should be informed that the response to alcohol may be exaggerated.

Use in Pregnancy - Pregnancy Category C. Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Care should be taken that there are sound indications for the use of these antidepressants in pregnancy.

Safe use of ALLEGRON during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing age, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

Daily feeding of nortriptyline at a diet level of 0.05 percent from Day 5 to Day 20 of the gestation period had no deleterious effects on foetal development of rabbits. Rats fed diets containing the equivalent of 30 mg per kg daily from the time of weaning until maturity and during breeding studies showed no indications of teratogenesis in the fetuses of two litters.

Use in children and adolescents (<18 years) – The safety and efficacy of ALLEGRON for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. ALLEGRON should not be used in this age group for the treatment of depression or other psychiatric disorders.

The use of ALLEGRON in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If the drug is given to overactive or agitated patients, increased anxiety and agitation may occur. In manic depressive patients, ALLEGRON may cause symptoms of the manic phase to emerge. Troublesome patient hostility may be aroused by the use of ALLEGRON. Epileptiform seizures may accompany its administration, as is true of other drugs of its class.

When it is essential, the drug may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery.

The possibility of a suicidal attempt by depressed patients remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time.

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

Drug Interactions - Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added or deleted from the drug regimen. Serious anticholinergic symptoms (severe dry mouth, urinary retention, blurred vision) have been associated with elevations in the serum levels of the tricyclic antidepressant when cimetidine is added to the drug regimen. In addition, higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. Alternatively, decreases in the steady-state serum concentration of the tricyclic antidepressant have been reported in well-controlled patients on concurrent therapy, on discontinuance of cimetidine.

The therapeutic efficacy of the tricyclic antidepressant may be compromised in these patients as cimetidine is discontinued. Several of the tricyclic antidepressants have been cited in these reports.

There have been greater than two-fold increases in previously stable plasma levels of other antidepressants, including nortriptyline, when PROZAC 20 (fluoxetine hydrochloride), has been administered in combination with these agents. Fluoxetine and its active metabolite, norfluoxetine, have a long half-life (4 to 16 days for norfluoxetine) which might affect strategies during conversion from one drug to the other.

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Close supervision and careful adjustment of the dosage are required when ALLEGRON is used with other anticholinergic drugs and sympathomimetic drugs.

A case of significant hypoglycaemia has been reported in a Type II diabetic patient maintained on chlorpropamide (250 mg/day) after the addition of nortriptyline (125 mg/day).

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC and lower clearance of nortriptyline.

Guanethidine and similar agents, thyroid medication, alcohol - see PRECAUTIONS.

Drugs metabolised by P450IID6 - A subset (3% to 10%) of the population has reduced activity of certain drug metabolising enzymes such as cytochrome P450 isoenzyme P450IID6. Such individuals are referred to as "poor metabolisers" of drugs such as debrisoquin, dextromethorphan and the tricyclic antidepressants. These individuals may have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses. In addition, certain drugs that are metabolised by this isoenzyme, including many antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors and others), may inhibit the activity of this isoenzyme, and thus may make normal metabolisers resemble poor metabolisers with regard to concomitant therapy with other drugs metabolised by this enzyme system, leading to drug interactions.

Concomitant use of tricyclic antidepressants with other drugs metabolised by cytochrome P450IID6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Therefore, co-administration of tricyclic antidepressants with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine and Type 1C antiarrhythmics (eg. propafenone, flecainide and encainide), or that inhibit this enzyme (eg. quinidine), should be approached with caution.

ADVERSE REACTIONS

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

Cardiovascular - Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric - Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurological - Numbness, tingling, paraesthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus.

Anticholinergic - Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic - Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); oedema (general or of face and tongue), drug fever, cross sensitivity with other tricyclic drugs.

Haematologic - Bone marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal - Nausea and vomiting, anorexia, epigastric distress, diarrhoea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus.

Endocrine - Gynaecomastia in the male; breast enlargement and galactorrhoea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other - Jaundice (simulating obstructive); altered liver function, hepatitis and liver necrosis; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms - Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

ALLEGRON is not recommended for children.

ALLEGRON is administered orally in the form of tablets. Lower than usual dosages are recommended for elderly patients and adolescents. The dosage for outpatients should also be lower than that for hospitalised patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

If a patient develops minor adverse reactions, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Usual Adult Dose - 25 mg 3 or 4 times daily; dosage should begin at a low level and be increased as required. Doses above 100 mg per day are not recommended.

Use in children and adolescents (<18 years) – The safety and efficacy of ALLEGRON for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. ALLEGRON should not be used in this age group for the treatment of depression or other psychiatric disorders (see PRECAUTIONS).

Elderly Patients - 25 to 50 mg per day, in divided doses.

Plasma Levels - Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150 mcg/L. Higher concentrations may be associated with more adverse experiences. Plasma concentrations are difficult to measure, and physicians should consult with the laboratory professional staff.

Older patients have been reported to have larger plasma concentrations of the active nortriptyline metabolite 10-hydroxy-nortriptyline. In one case, this was associated with apparent cardiotoxicity despite nortriptyline concentrations within the "therapeutic range". Clinical findings should predominate over plasma concentrations as primary determinants of dosage changes.

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 centre 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. Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia or many of the symptoms listed under ADVERSE REACTIONS.

Treatment -- In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal.

Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing charcoal.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate. It is important to monitor and manage serum electrolyte levels. Refractory arrhythmias may respond to propranolol, bretylium, or lignocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose. Seizures may respond to diazepam. Phenytoin has pharmacologic properties that may be helpful in dealing with both the seizures and cardiac rhythm disturbances of tricyclic antidepressant overdose. Although the prophylactic use of phenytoin has been suggested, it is not yet of proven value.

Diuresis and dialysis remove little of the tricyclic antidepressant present in the body of a patient who has taken an overdose. Haemoperfusion is of unproven benefit. The patient who has taken a tricyclic overdose should be monitored closely, at least until the QRS duration is normal.

HOW SUPPLIED

10 mg plain, round, white tablets, blister pack, 50 tablets.

25 mg orange round tablets with a scoreline on one side, blister pack, 50 tablets.

NAME AND ADDRESS OF SPONSOR

Aspen Pharmacare Australia Pty Ltd
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