AMIROL

Amitriptyline hydrochloride

Name of Medicine

Amirol 10 Film coated tablets 10 mg
Amirol 25 Film coated tablets 25 mg

Presentation

AMIROL 10mg tablets are blue, film coated biconvex tablets, 9/32" diameter. Each tablet contains 10mg amitriptyline hydrochloride.

AMIROL 25mg tablets are yellow, film coated biconvex tablets, 9/32" diameter. Each tablet contains 25mg amitriptyline hydrochloride.

For both strengths do not halve tablet, dose equivalent when the tablet is divided has not been established.

Uses

Actions

Amitriptyline is a potent antidepressant with sedative properties. The mechanism of action in humans is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system. In broad clinical use amitriptyline has been found to be well tolerated.

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.

Pharmacokinetics

Absorption

Appears in plasma within 30 to 60 minutes after oral ingestion and 5 to 10 minutes after intramuscular injection. Approximately 62% of the radioactive doses of ^{14}C was recovered in human urine after oral or intravenous administration. Plasma levels are very low with broad peaks ranging from 2-12 hours after administration.

Metabolism

In one study, 12 normal subjects received 25mg of amitriptyline t.i.d.; plasma amitriptyline levels were maximal (62 ± 20 ng/ml) at 4 hours post therapy. In another study in which 12 normal subjects received 25mg amitriptyline t.i.d. for 2 weeks, the plasma half-life averaged 30 hours.

Studies in humans following oral administration of ^{14}C-labelled medicine indicated that amitriptyline is rapidly absorbed and metabolised. 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 medicine was excreted within 24 hours.

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

Excretion

Urine

Following an intravenous dose, an average total of 62.9% of radioactivity was excreted in 7 days, with 25.1% being excreted in the first 24 hours. Following oral administration, an average total of 63.0% of radioactivity was excreted in 7 days, with 27.0% excreted in the first 24 hours.

Faeces

Following oral administration ^{14}C-labelled tablets, excretion of radioactivity was calculated to be 10.5% (average) over 7 days; after intravenous administration, an average of 12.7% was recovered in the faeces in 7 days.

Bile

Animal studies show that amitriptyline and its metabolites are excreted in the bile.

Milk

In one report, following 100 mg/day of oral amitriptyline, levels of 135-151 ng/ml were found in the breast milk of a lactating patient.

Indications

AMIROL is recommended for the treatment of depression.

Dosage and Administration

Depression

Dosage Considerations

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.
Oral Dosage.
Do not halve tablet, dose equivalent when the tablet is divided has not been established.

Initial Adult Dosage for Outpatients

75mg of amitriptyline a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150mg 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.

Alternate methods of initiating therapy in outpatients are to begin therapy with 50 to 100mg amitriptyline preferably in the evening or at bedtime; this may be increased by 25 to 50mg as necessary to a total of 150mg per day. Initiate therapy with one 75mg capsule or tablet preferably in the evening or at bedtime and increase, if necessary, to two, or one in the morning and one in the evening.

Dosage for Hospitalised Patients

100mg a day may be required initially. This can be increased gradually to 200mg a day if necessary. A small number of hospitalised patients may need as much as 300mg a day.

Dosage for Elderly Patients

In general, lower dosages are recommended for these patients. In those elderly patients who may not tolerate higher doses, 50mg daily may be satisfactory. The required daily dose may be administered either as divided doses or as a single dose preferably in the evening or at bedtime.

Adolescent Depression

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist.

Maintenance Dosage

The usual maintenance dose is 50 to 100mg amitriptyline per day. For maintenance therapy, the total daily dosage may be given in a single dose preferably in the evening or 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.

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. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.

Contraindications

- Amitriptyline is contraindicated for the treatment of depression in patients 12 years of age and under.
- Amitriptyline is contraindicated for the treatment of nocturnal enuresis.
- Amitriptyline is contraindicated in patients who have shown prior hypersensitivity to it.
- It should not be given concomitantly with a monoamine oxidase inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting medicines simultaneously. When it is desired to substitute amitriptyline for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. Amitriptyline should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

- This medicine is contraindicated for use during the acute recovery phase following myocardial infarction.
- See Use in Pregnancy under Warnings and Precautions.

Warnings and Precautions

Clinical Worsening and Suicide Risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, 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. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients 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 the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that amitriptyline is not approved for use in treating bipolar depression.

Information for Patients and Families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such

symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

General

Amitriptyline should be used with caution in patients with a history of seizures, in patients with impaired liver function 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. Discontinue the medicine several days before elective surgery if possible.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic medicines, particularly during hot weather.

The medicine may impair alertness in some patients; operation of automobiles and other activities made hazardous by diminished alertness should be avoided.

Cardiovascular Disorders

Amitriptyline should be used with caution in patients with cardiovascular disease, including heart failure, conduction disorders, (e.g. AV block grades I to III), or arrhythmias. Cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Tricyclic antidepressant medicines, including amitriptyline, particularly when given in high doses, have been reported to produce QTc prolongation, arrhythmias (including Torsades de pointes-TdP), sinus tachycardia, and prolongation of the conduction time. Myocardial Infarction and stroke have been reported with medicines of this class (See Adverse Events).

Amitriptyline should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age > 65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of amitriptyline, and the concomitant use of other QTc prolonging medicines (see Interactions). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping amitriptyline treatment or reducing the dose if the QTc interval is > 500ms or increases by > 60ms.

Endocrine Disorders

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

Central Nervous System Disorders

When amitriptyline is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated.

Paranoid delusions, with or without associated hostility, may be exaggerated. In any of these circumstances, it may be advisable to reduce the dose of amitriptyline or to use a major tranquillising medicine, such as perphenazine, concurrently.

Use in Pregnancy

Amitriptyline should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under the close supervision of a physician.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants in pregnancy.

Neonates should be observed if maternal use of amitriptyline has continued into the later stages of pregnancy, particularly into the third trimester.

Neonates exposed to tricyclic antidepressants, late in the third trimester have showed drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

Nursing Mothers

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 medicine.

Adverse Effects

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

Cardiovascular

Hypotension, syncope, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de pointes), , stroke, ECG changes (including QTc prolongation, non-specific ST and T wave changes, and AV conduction disorders such as heart block, bundle branch block and widened QRS complex).

CNS and Neuromuscular

Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; drowsiness; insomnia; nightmares; numbness; tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; coma; seizures; alteration in EEG patterns; extrapyramidal symptoms, including abnormal involuntary movements and tardive dyskinesia; dysarthria; tinnitus.

Anticholinergic

Dry mouth, blurred vision, mydriasis, disturbance of accommodation, increased intraocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, dilatation of urinary tract.

Allergic

Skin rash, urticaria, photosensitization, oedema of face and tongue.

Haematologic

Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal

Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhoea, parotid swelling, black tongue, rarely hepatitis (including altered liver function and jaundice).

Endocrine

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

Other

Dizziness, weakness, fatigue, headache, weight gain or loss, oedema, increased perspiration, urinary frequency, mydriasis, drowsiness, alopecia.

Withdrawal Symptoms

Abrupt cessation of treatment after prolonged administration 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.

Adverse Effects - Casual Relationship Unknown

The following additional adverse effects have been reported; however, a casual relationship to therapy with amitriptyline has not been established.

Body as a Whole

Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

Interactions

Medicines that can prolong the QTc interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QT interval.

Fluoxetine

Fluoxetine markedly inhibits Cytochrome P450 2D6, which is involved in the metabolism of a number of tricyclic antidepressants including amitriptyline. Patients should be monitored for increased antidepressant plasma levels and toxicity when fluoxetine is used concurrently. Adjustment of the antidepressant dosage maybe necessary.

Other Antidepressant Medicines

The potency of amitriptyline is such that addition of other antidepressant medicines 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 hydrochloride and other antidepressant medicines should be undertaken only with due recognition of the possibility of potentiation and with a thorough knowledge of the pharmacology of both medicines. There have been no reports of untoward events when patients receiving amitriptyline were changed immediately to protriptyline or vice versa.

Guanethidine

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

Anticholinergic Agents/Sympathomimetic Medicines

When amitriptyline is given with anticholinergic agents or sympathomimetic medicines, including epinephrine combined with local anaesthetics, close supervision and careful adjustment of dosage are required. Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type medicines.

Cimetidine

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.

Central Nervous System Depressants

Amitriptyline may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1g of ethchlorvynol and 75-150mg of amitriptyline.

Disulfiram

Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Electroshock Therapy

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.

Overdosage

Cardiovascular

Cardiovascular system: hypotension, tachycardia, QTc prolongation, arrhythmias (including Torsades de pointes), conduction disorders, shock, heart failure, in very rare cases cardiac arrest.

Manifestations

High doses may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Over-dosage may cause drowsiness; hypothermia; tachycardia and other arrhythmic abnormalities, such as bundle branch block; ECG evidence of impaired conduction; congestive heart failure; dilated pupils; disorders of ocular motility; convulsions; severe hypotension; stupor; coma and polyradiculoneuropathy; constipation.

Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under Adverse Effects.

All patients suspected of having taken an overdose should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. Empty the stomach as quickly as possible by emesis followed by gastric lavage upon arrival at the hospital. Following gastric lavage, activated charcoal may be administered. Twenty to 30g of activated charcoal may be given every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function instituted if there is any sign of abnormality. Maintain an open airway and adequate fluid intake; regulate body temperature.

The intravenous administration of 1-3mg of physostigmine salicylate has been reported to reverse the symptoms of tricyclic antidepressant poisoning. Because physostigmine is rapidly metabolised, the dosage of physostigmine should be repeated as required particularly if 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.

Standard measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. Should cardiac failure occur, the use of digitalis should be considered. Close monitoring of cardiac function of not less than five days is advisable.

Anticonvulsants may be given to control convulsions. Amitriptyline increases the CNS depressant action but not the anticonvulsant action of barbiturates; therefore, an inhalation anaesthetic, diazepam, or paraldehyde is recommended for control of convulsions.

Dialysis is of no value because of low plasma concentrations of the medicine.

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of medicine.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

AMIROL 10mg tablets: Blister packs of 30 tablets.
AMIROL 25mg tablets: Blister packs of 30 tablets.

Further Information

Nil.

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