Injection/Tablets/Syrup/Capsules

TRYPTIZOL®

(Amitriptyline hydrochloride)

TRYPTIZOL® (amitriptyline hydrochloride) is a potent antidepressant with sedative properties. The 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. In broad clinical use, TRYPTIZOL has been found to be well tolerated.
TRYPTIZOL has also been found effective in the treatment of enuresis in some cases where organic pathology has been excluded. The mode of action of TRYPTIZOL in enuresis is not known. However, TRYPTIZOL does have anticholinergic properties and drugs of this group, such as belladonna, have been used in the treatment of enuresis.

INDICATIONS

TRYPTIZOL is recommended in:
- The treatment of depression.
- Nocturnal enuresis where organic pathology has been excluded.

DOSAGE AND ADMINISTRATION

TRYPTIZOL is supplied as:
Tablets: 10,25,50 and 75 mg amitriptyline hydrochloride.
Syrup: 17 mg amitriptyline pamoate (equivalent to 10 mg amitriptyline) per each 5 ml.
Capsules: 75 mg amitriptyline hydrochloride (as a pelleted formulation).
The pelleted formulation has a slower in vitro rate of dissolution than the tablet form, which extends the period over which the drug is released for absorption.
An injectable formulation for intramuscular or intravenous use is formulated as follows, with each milliliter containing: 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

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: Initial Dosage for Outpatient Adults - 75 mg of TRYPTIZOL a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg a day. Increases are made preferably in the late afternoon and/or bedtime doses. The sedative effect is usually rapidly apparent. The antidepressant activity may be evident within 3 or 4 days or may take up to 30 days to develop adequately.
Alternate methods of initiating therapy in outpatients are:
Begin therapy with 50 to 100 mg TRYPTIZOL preferably in the evening or at bedtime; this may be increased by 25 to 50 mg as necessary to a total of 150 mg per day.
Initiate therapy with one 75 mg 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 Hospitalized Patients - 100 mg a day may be required 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.
Dosage for Elderly Patients - In general, lower dosages are recommended for these patients. In those elderly patients who may not tolerate higher doses, 50 mg 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.

MAINTENANCE DOSAGE: The usual maintenance dose is 50 to 100 mg TRYPTIZOL 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.

PARENTERAL DOSAGE: The parenteral route of administration is often desirable in the depressed patient because of:
1. inability or refusal to take oral medicine
2. suicidal tendencies (see PRECAUTIONS)
3. need for rapid control of symptoms when electroshock therapy is either contraindicated or refused.
Initially, 20 to 30 mg (2 to 3ml) four times a day.
It may be advisable to administer TRYPTIZOL intramuscularly or intravenously for the first week or so. In this way, the physician will have optimal control of initial therapy.
Oral therapy with TRYPTIZOL can be substituted when the pattern of response has been determined and the more severe aspects of the depression have been relieved. In uncooperative or undependable patients, the use of Injection TRYPTIZOL will help to insure proper medication.
When Injection TRYPTIZOL is used for initial therapy in patients unable or unwilling to take oral medication, the tablets or capsules should replace the injection as soon as possible.

ENURESIS: A dose of 10 mg at bedtime has been found effective in children under six years of age. In older children, the dosage should be increased as necessary according to weight and age. Children 6 to 10 years of age may receive 10 to 20 mg of TRYPTIZOL per day. In the age group from 11 to 16 a dose of 25 to 50 mg may be required.
Most patients respond in the first few days of therapy. In those who do respond, the tendency is for increasing, continued improvement as the period of treatment is extended. Continued treatment is usually required to maintain the response until control is established.
The doses of TRYPTIZOL recommended in the treatment of enuresis are low compared with those used in the treatment of depression, even allowing for differences in age and weight. This recommended dose must not be exceeded. This medication should be kept out of reach of children.

PLASMA LEVELS: Because of the wide variation in the absorption and distribution of tricylic 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 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 drugs 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.
Amitriptyline is contraindicated in patients taking cisapride because of the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac arrhythmias and conduction system disturbances.
This drug is not recommended for use during the acute recovery phase following myocardial infarction.

See ***USE IN PREGNANCY*** under PRECAUTIONS.

PRECAUTIONS

***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 drug several days before elective surgery if possible.
Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.
The drug may impair alertness in some patients; operation of automobiles and other activities made hazardous by diminished alertness should be avoided.
***Clinical worsening and suicide*:** 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 behaviors (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 dosage 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/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.
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 nonpsychiatric. 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 or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behavior, 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 TRYPTIZOL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Cardiovascular disorders: Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including amitriptyline HCl, 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.
Endocrine disorders: Close supervision is required when amitriptyline is given to hyperthyroid patients or those receiving thyroid medication.
Central nervous disorder: The possibility of suicide in depressed patients remains during treatment. Patients should not have access to large quantities of this drug during treatment.
When amitriptyline HCl is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated. Likewise, in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase. 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 an antipsychotic drug, concurrently.
***Use in children*:** Tryptizol is not recommended for the treatment of depression in persons below the age of 18 years. Any such use should be carefully monitored by a physician, and consideration be given to drug withdrawal/cessation if symptoms suggestive of suicidality and/or lack of therapeutic efficacy are observed.
Use in pregnancy: There are no well-controlled studies in pregnant women; therefore, in administering the drug to pregnant patients or women who may become pregnant, the potential benefits must be weighed against the possible hazards to mother and child.
***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 drug.

DRUG INTERACTIONS

***Other antidepressant drugs*:** The potency of TRYPTIZOL is such that addition of other antidepressant drugs generally does not result in any additional therapeutic benefit. Untoward reactions have been reported after the combined use of antidepressant agents having varying modes of activity. Accordingly, combined use of amitriptyline hydrochloride and other antidepressant drugs should be undertaken only with due recognition of the possibility of potentiation and with a thorough knowledge of the pharmacology of both drugs. There has been no reports of untoward events when patients receiving amitriptyline HCl were changed immediately to protriptyline or vice versa.
***Guanethidine*:** Amitriptyline may block the antihypertensive action of guanethidine or similarly acting compounds.
Anticholinergic agents/sympathomet ic drugs: When amitriptyline is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosage are required. Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.
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 1 g of ethchlorvynol and 75-150 mg 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.
***Analgesics*:** Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.
***Drug metabolised by cytochrome P450 2D6*:** Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 (e.g. quinidine; cimetidine) and those that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics, propafenone and flecainide) may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. 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.
Although P450 2D6 metabolizes amitriptyline to several metabolites, it has been noted that in vitro studies have shown metabolism of amitriptyline by multiple P450 enzymes including P450 3A4, 2C19 and 1A2 and clinical studies have shown inhibitors and inducers of P450 3A4 to alter amitriptyline concentrations. With respect to P450 3A4, inhibitors of the enzyme (e.g., ketoconazole, ritonavir, etc.) may increase plasma concentrations of amitriptyline and increase its action. In addition, inducers of the enzyme (e.g., carbamazepine, phenytoin, St John's wort, etc.) may increase its metabolism and decrease its effect. Care should be taken when administering amitriptyline to patients receiving agents which inhibit or induce P450 enzymes.
***Serotonin syndrome*:** The "serotonin syndrome" (alterations in cognition, behavior, autonomic nervous system function, and neuromuscular activity) has been reported with amitriptyline when given concomitantly with other serotonin-enhancing drugs.

SIDE EFFECTS

Note: Included in the listing which follows are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.
***Cardiovascular*:** Hypotension, syncope, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, non-specific ECG changes and changes in AV conduction.
***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, pruritus, urticaria, photosensitization, edema of face and tongue.
***Hematologic*:** Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia.
***Gastrointestinal*:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, 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, edema, increased perspiration, urinary frequency, 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.
***In Enuresis*:** The doses of TRYPTIZOL recommended in the treatment of enuresis are low compared with those used in the treatment of depression, even allowing for differences in age and weight. Side effects consequently are even less frequent than when the drug is used in treating depression.
The most common side effects are:
1. Drowsiness. This is unlikely to be a disadvantage since the drug is being taken at bed time, and in fact may be an asset.
2. Anticholinergic effects. These also may be an asset, as anticholinergic drugs have long been used in the treatment of enuresis.
The only other side effects which have been encountered with the doses of TRYPTIZOL recommended for enuresis have been mild sweating and itching, but these have been infrequent.

POSTMARKETING ADVERSE EVENTS

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

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As management of overdose 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 overdosage 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 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 this 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 a 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 pCO2 <20 mmHg 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 close 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 child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

AVAILABILITY

Tablets TRYPTIZOL of 10 mg are supplied in packages of 100 and 1000 tablets.
Tablets TRYPTIZOL of 25 mg are supplied in packages of 30 and 1000 tablets.

Storage Conditions: Store in a dry place below 30˚C, protected from light. Do not refrigerate

Keep out of reach and sight of children.

Do not use after expiry date.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold you the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by
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