PRODUCT MONOGRAPH

TRIMIPRAMINE

Trimipramine Tablets BP

12.5, 25, 50 and 100 mg Trimipramine (as maleate)

Trimipramine Capsules

75 mg Trimipramine (as maleate)

Tricyclic Antidepressant

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THERAPEUTIC CLASSIFICATION

Tricyclic Antidepressant

ACTIONS AND CLINICAL PHARMACOLOGY

Trimipramine is a tricyclic antidepressant with sedative properties. It also has anti-cholinergic properties, and potentiates sympathetic responses, presumably by blocking the re-uptake of noradrenaline which has been released by the presynaptic neurones. Trimipramine has a quinidine-like effect on the heart and produces ECG and EEG changes similar to those of other tricyclic antidepressants.

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of trimipramine following a single 150 mg (2 x 75 mg capsules) oral dose of TRIMIPRAMINE and SURMONTIL were measured and compared. The results are summarized as follows:

Geometric Mean Arithmetic Mean (C.V.)			
Parameter	**Trimipramine**	**Surmontil**	**Ratio of Means (%)**
AUC_T (ng·hr/mL)	1037 1235 (66)	1015 1266 (75)	102.2
AUC_I (ng·hr/mL)	1165 1393 (67)	1143 1447 (78)	101.9
C_{max} (ng/mL)	85.6 94.2 (42)	81.7 92.7 (58)	104.8
T_{max}* (hr)	3.2 (1.2)	3.0 (1.5)	—
$t_{1/2}$* (hr)	25.3 (13.3)	26.4 (14.3)	—

For the T_{max} and $t_{1/2}$ parameters, these are the arithmetic means (standard deviations).

INDICATIONS

TRIMIPRAMINE (trimipramine) is indicated in the drug treatment of depressive illness. It is effective in endogenous depression.

CONTRAINDICATIONS

TRIMIPRAMINE (trimipramine) is contraindicated in cases of known hypersensitivity to the drug. The possibility of cross-sensitivity with other dibenzazepine compounds should also be kept in mind.

Trimipramine should not be administered concomitantly or within 2 weeks of treatment with an MAO inhibitor. Hyperpyretic crises, severe convulsions and death have occurred in patients receiving MAO inhibitors and tricyclic antidepressants. When substituting trimipramine for an MAO inhibitor, treatment should be started with small doses and increased progressively, depending on tolerance and response. Because of its anticholinergic properties, trimipramine is contraindicated in patients with narrow angle glaucoma and prostatic hypertrophy.

It is also contraindicated during the acute recovery phase following myocardial infarction and in the presence of acute congestive heart failure.

WARNINGS

Tricyclic antidepressants, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. A few instances of unexpected death have been reported in patients with cardiovascular disorders.

Myocardial infarction and stroke have also been reported with drugs of this class. Therefore, TRIMIPRAMINE (trimipramine) should be administered with caution to patients with a history of cardiovascular disease, those with circulatory lability and elderly patients. In such cases, treatment should be initiated with low doses, with progressive increases only if required and well tolerated.

Close supervision is required for hyperthyroid patients or those receiving thyroid medication, because of the possibility of cardiovascular toxicity.

Patients receiving trimipramine should be advised against driving or engaging in activities requiring mental alertness and physical coordination until their response to the drug has been well established. They should also be cautioned that the response to alcohol might be potentiated.

Use in pregnancy: The safety of trimipramine during pregnancy and lactation has not been established and, therefore, it should not be used in women of child-bearing potential or nursing mothers, unless the potential benefits outweigh the possible hazards to mother and child.

Use in children: Trimipramine is not recommended for use in children, since safety and effectiveness in this age group have not been established.

PRECAUTIONS

The possibility of suicide in seriously depressed patients may remain until significant remission occurs. Such patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization and/or concomitant ECT. This type of patient should not have easy access to large quantities of trimipramine.

TRIMIPRAMINE (trimipramine) may precipitate or aggravate psychotic manifestations in schizophrenic patients and hypomanic or manic episodes in manic-depressive patients. This may require reduction of dosage, discontinuation of the drug, and/or administration of an antipsychotic agent.

Since tricyclic agents are known to reduce the seizure threshold, trimipramine should be administered with caution to patients with a history of convulsive disorders. Concurrent administration of ECT and trimipramine may be hazardous and, therefore, such treatment should be limited to patients for whom it is essential.

Tricyclic antidepressants may give rise to paralytic ileus, particularly in the elderly and in hospitalized patients. Therefore, appropriate measures should be taken if constipation occurs. Combined use with other drugs acting on the central nervous system, such as alcohol, barbiturates and other CNS depressants, should be undertaken with recognition of the possibility of potentiation.

Tricyclic drugs may also block the antihypertensive effects of guanethidine and related compounds. When trimipramine is given with anticholinergic agents or sympathomimetic drugs, close supervision and careful adjustment of dosages are required. Caution is also advised if patients receive large doses of ethchlorvynol and tricyclic antidepressants concurrently.

Trimipramine should be used with caution in patients with impaired liver function or with a history of hepatic damage or blood dyscrasias. Periodic blood counts and liver function test should be performed when patients receive trimipramine in large doses or over prolonged periods.

ADVERSE REACTIONS

The similarities among the tricyclic anti depressant drugs require that each of the reactions be considered when TRIMIPRAMINE (trimipramine) is administered. Some of the adverse reactions included in this listing have not, in fact, been reported with trimipramine.

Behavioural: Drowsiness (mainly during initial therapy), fatigue, excitement, agitation, restlessness, insomnia, shifts to hypomania or mania, activation of latent psychosis, disorientation, confusion, hallucinations, delusions, nightmares, jitteriness, anxiety, giddiness.

Neurological: Seizures, incoordination, ataxia, tremors, dystonia, extrapyramidal symptoms, numbness, tingling, paresthesias of the limbs, peripheral neuropathy, headache, alteration in EEG patterns, tinnitus, slurred speech.

Autonomic: Dry mouth, urinary retention, constipation, paralytic ileus, disturbance of accommodation, blurred vision, precipitation of latent and aggravation of existing glaucoma, mydriasis, vertigo, syncope.

Cardiovascular: Hypotension, hypertension, palpitations, tachycardia, arrhythmias, prolonged conduction time and asystole, heart block, fibrillation, myocardial infarction, stroke and sudden death in patients with cardiovascular disorders. The ECG changes include flattening or inversion of T-waves, depressed S-T segment and bundle branch block.

Endocrine: Changes in libido, weight gain or loss, testicular swelling, gynecomastia and impotence in the male, breast enlargement and galactorrhea in the female, elevation or lowering of blood sugar levels.

Allergic: Skin rash, edema, urticaria, pruritus, and photosensitivity.

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

Gastrointestinal: Nausea, epigastric distress, heartburn, vomiting, anorexia or increased appetite, stomatitis, peculiar taste, diarrhea.

Miscellaneous: Obstructive jaundice, weakness, urinary frequency, increased perspiration, alopecia, parotid swelling, black tongue.

Withdrawal Symptoms: Abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise. These symptoms are not indicative of addiction.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Drowsiness, mydriasis, dysarthria, general weakness, excitement, agitation, hyperactive reflexes, muscle spasms and rigidity, hypothermia, hyperpyrexia, vomiting, perspiration, rapid thready pulse, convulsions, severe hypotension, hypertension, tachycardia, disturbances of cardiac conduction, arrhythmia, congestive heart failure, circulatory collapse, respiratory depression and coma. In patients with glaucoma, even average doses may precipitate an attack.

Treatment: There is no specific antidote and treatment is essentially symptomatic and supportive. Cardiac arrhythmias and CNS involvement pose the greatest threat and may occur suddenly, even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdosage of trimipramine, particularly children, should be hospitalized and kept under close surveillance.

The stomach should be emptied as quickly as possible by gastric lavage or, if the patient is alert, by induced emesis. It may be helpful to leave the tube in the stomach, with irrigation (with an electrolyte-balanced fluid) and continual aspiration of stomach contents possibly promoting more rapid elimination of the drug from the body. If the patient is not alert, a cuffed endotracheal tube should be inserted before lavage is performed and emesis should not be induced. Administration of activated charcoal may help reduce absorption of trimipramine. In case of severe intoxication, dialysis may be undertaken, although the efficacy of such a procedure in tricyclic poisoning is doubtful due to low plasma concentrations of these drugs.

Treatment should be designed to insure maintenance of the vital functions. An open airway should be maintained. Failing respiration must be maintained by artificial means, but respiratory stimulants should not be used. Hyperpyrexia should be controlled by external measures, such as ice packs and cooling sponge baths. Bladder catheterization should be performed in the unconscious patient.

ECG monitoring in an intensive care unit is recommended in all patients, particularly in the presence of EGG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal.

Because of its effect on cardiac conduction, digitalis should be used only with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

External stimulation should be minimized to reduce the tendency to convulsions. If an anticonvulsant is necessary, administer intravenous diazepam; barbiturates should be avoided since they intensify respiratory depression, particularly in children, and aggravate hypotension and coma.

Shock should be treated with supportive measures, such as intravenous fluids, oxygen and corticosteroids. Pressor agents, such as noradrenaline (but not adrenaline), are rarely indicated and should be given only after careful consideration and under continuous monitoring.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the cardiovascular and GNS anticholinergic manifestations of tricyclic overdosage. The recommended dosage in adults has been 1 to 2 mg in very slow intravenous injection.

In children, the initial dosage should not exceed 0.5 mg and should be adjusted to age and response. Since physostigmine has a short duration of action, administration may have to be repeated at 30 to 60-minute intervals.

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered.

DOSAGE AND ADMINISTRATION

As with other psychotropic drugs, the dosage of TRIMIPRAMINE (trimipramine) should be adapted to the requirements of each individual patient. Treatment should be initiated at the lowest recommended dose and increased gradually, noting carefully the clinical response and any evidence of intolerance.

It should be kept in mind that a lag in therapeutic response usually occurs at the onset of therapy, lasting from several days to a few weeks. Increasing the dosage does not normally shorten this latent period and may increase the incidence of side effects.

Initial Dosage: Adults: The recommended initial dose is 75 mg daily in two or three divided doses. Initial tolerance may be tested by giving the patient 25 mg in the evening of the first day. The initial dose should be increased by 25 mg increments, usually up to 150 mg daily, preferably by adding to the late afternoon and/or bedtime doses. In the case of severely depressed patients, a higher initial dose of 100 mg daily in two or three divided doses may be indicated. The usual optimal dose is 150 to 200 mg daily, but some patients may require up to 300 mg daily, depending on tolerance and response of each individual patient.

Elderly or debilitated patients: In these patients, it is advisable to give a test dose of 12.5 to 25 mg and, after 45 minutes, examine the patient sitting and standing to check for orthostatic hypotension. Initial doses should usually be no more than 50 mg a day in divided doses, with weekly increments of no more than 25 mg a week, leading to a usual therapeutic dose range of 50 to 150 mg a day.

Blood pressure and cardiac rhythm must be checked frequently, particularly in patients who have unstable cardiovascular function.

Maintenance Dosage: Once a satisfactory response has been obtained, the dosage should be adjusted to the lowest level required to maintain symptomatic relief. Medication should be continued for the expected duration of the depressive episode in order to minimize the possibility of relapse following clinical improvement.

When a maintenance dosage has been established as described above, trimipramine may be administered in a single dose before bedtime provided such a dosage regimen is well tolerated.

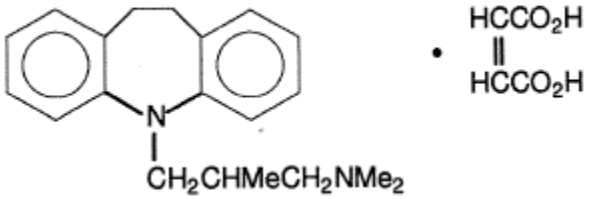
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: trimipramine maleate

Chemical Name: 3-(10, 11-dihydro-5H-dibenz[b,f]azepin-5-yl)-methylpropyl-dimethylamine hydrogen maleate

Structural Formula:



Molecular Formula: $C_{20}H_{26}N_2,C_4H_4O_4$

Molecular Weight: Trimipramine - 294.4
Trimipramine maleate - 410.5

Description: Trimipramine maleate is a white or almost white, crystalline powder. It is slightly soluble in water and in ethanol; freely soluble in chloroform; and practically insoluble in ether.

Composition

Tablets: In addition to trimipramine maleate, each tablet contains the non-medicinal ingredients microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and FD&C red #3.

Capsules: In addition to trimipramine maleate, each capsule contains the non-medicinal ingredients lactose, croscarmellose sodium, stearic acid, magnesium stearate, gelatin, sodium lauryl sulfate, sodium metabisulfite, FD&C red #3, D&C yellow #10, titanium dioxide and

FD&C blue #1. The edible black printing ink on the capsule shell contains the non-medicinal ingredients synthetic black iron oxide, FD&C blue #1, FD&C blue #2, FD&C red #40, D&C yellow #10, pharmaceutical glaze, alcohol and propylene glycol.

Stability and Storage Recommendations

Protect from light. Store at controlled room temperature 15-30°C (59-86°F).

AVAILABILITY OF DOSAGE FORMS

Tablets

TRIMIPRAMINE (Trimipramine Tablets BP), 12.5 mg: each round, pink, biconvex, film-coated tablet, engraved "A" on one side, contains trimipramine maleate equivalent to 12.5 mg of trimipramine.

TRIMIPRAMINE (Trimipramine Tablets BP), 25 mg: each round, pink, biconvex, film-coated tablet, engraved "25 on one side, contains trimipramine maleate equivalent to 25 mg of trimipramine.

TRIMIPRAMINE (Trimipramine Tablets BP), 50 mg: each round, pink, biconvex, film-coated tablet engraved "50" on one side contains trimipramine maleate equivalent to 50 mg of trimipramine.

TRIMIPRAMINE (Trimipramine Tablets BP), 100 mg: each round, pink, biconvex, film-coated tablet scored and engraved "100" on one side contains trimipramine maleate equivalent to 100 mg of trimipramine.

Capsules

TRIMIPRAMINE (Trimipramine Capsules), 75 mg: each hard gelatin capsule with buff body and pink cap, printed "75", contains trimipramine maleate equivalent to 75 mg of trimipramine.

TRIMIPRAMINE tablets and capsules are available in bottles of 100, 500 and 1000.

PHARMACOLOGY

Like other tricyclic antidepressants trimipramine antagonizes reserpine induced ptosis, hypothermia and depression in mice and rats and post electroshock depression in the rabbit and in the rat. It potentiates the narcotic effect of ether and hexobarbital and depresses spontaneous activity in mice, but does not cause catalepsy and does not block significantly conditioned avoidance responses.

Trimipramine protects against maximal electroshock-induced convulsions, but lowers the threshold for metrazol-induced convulsions. In 'in vitro' tests, anti-serotonin and antihistaminic activities have been demonstrated. Trimipramine also possesses antiemetic and analgesic properties.

Like other tricyclic drugs, trimipramine potentiates the pressor effect of directly acting sympathomimetic amines. The drug also has anticholinergic properties.

Trimipramine lowers the blood pressure in anesthetized dogs and induces tachycardia of short duration. Like other tricyclic agents, trimipramine exerts a quinidine-like myocardial depressant effect in chloralose-anesthetized dogs.

TOXICOLOGY

Acute Toxicity: The LD_{50} of trimipramine in the mouse is 42 mg/kg intravenously, 425 mg/kg per os, 285 mg/kg subcutaneously, and 145 mg/kg intraperitoneally. At toxic doses, the animals exhibited sporadic episodes of convulsions followed by depression. They died from respiratory arrest during a final convulsive attack.

The intravenous LD_{50} of trimipramine in the rabbit is 27 (25-30) mg/kg.

Subacute Toxicity: Trimipramine was well tolerated by rats when administered at a daily oral dose of 20 to 40 mg/kg for one month.

Administered to dogs at a daily oral dose of 15 and 30 mg/kg for one month, trimipramine was well tolerated, and failed to produce any damage to vital organs.

Chronic Toxicity: A chronic toxicity study using daily oral doses of 6.67, 20 and 60 mg/kg of trimipramine for 52 weeks in rats and for 26 weeks in dogs, produced at the lowest level no deleterious effect on survival, weight gain, appearance, and behaviour. Hematology, organ weights in both species and urinalysis, SGPT, SGOT, serum alkaline phosphatase, and blood urea nitrogen in the dogs were within normal limits. Dose-related mild liver and kidney changes were observed in both species; the incidence of kidney changes being somewhat higher in the rat with a predominance at the 20 mg/kg dose level.

Reproduction Studies: There was no difference in the average size of litters produced by female rats, given 0, 7, and 50 mg/kg daily from the sixth to the sixteenth day of pregnancy. The administration of 0 and 500 mg/kg daily in the diet to rats of both sexes for one month before mating and then throughout the ensuing gestations and lactations resulted in comparable average litter sizes; there was no adverse effect on fertility, nor any evidence of embryopathic effects. Oral dosages of 0, 6 to 7, and 14 to 28 mg/kg administered to pregnant rabbits did not appear to produce significant teratogenic effects, but the results of this study were inconclusive.

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