PRODUCT MONOGRAPH

RHOTRIMINE®
(Trimipramine)

12.5, 25, 50 and 100 mg Tablets
75 mg Capsules

Tricyclic Antidepressant

sanofi-aventis Canada Inc.
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Date of Preparation:
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ACTION

RHOTRIMINE (trimipramine) is a tricyclic antidepressant with sedative properties. It has also anticholinergic properties and potentiates the sympathetic responses, presumably by blocking the re-uptake of norepinephrine which has been released by the presynaptic neurones. Trimipramine has a quinidine-like effect on the heart and produces E.K.G and E.E.G. changes similar to those of other tricyclic antidepressants.

INDICATIONS

RHOTRIMINE (trimipramine) is indicated in the drug treatment of depressive illness. It is particularly effective in endogenous depression. It may also be useful in some patients with neurotic depression.

CONTRAINDICATIONS

RHOTRIMINE (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.

Monoamine oxidase inhibitors should not be administered concomitantly with RHOTRIMINE and a two-week delay is recommended before using the drug in patients who have received an MAO inhibitor. Treatment with RHOTRIMINE should be started with small doses and increased progressively, depending on tolerance and response.

Because of its anticholinergic properties, RHOTRIMINE 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, RHOTRIMINE (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.

Patients receiving RHOTRIMINE should be advised against driving or engaging in activities requiring mental alertness and physical co-ordination 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 childbearing potential or nursing mothers, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus.

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

PRECAUTIONS

RHOTRIMINE (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.

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.

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 tests should be performed when patients receive trimipramine in large doses or over prolonged periods.

ADVERSE REACTIONS

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

Behavioral
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, dizziness, dysarthria, ataxia, tremor, 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 accomodation, blurred vision, precipitation of latent and aggravation of existing glaucoma, mydriasis, vertigo, syncope.

Cardiovascular
Palpitations, tachycardia, orthostatic hypotension, hypertension, a quinidine-like effect and other reversible EKG changes such as flattening or inversion of T-waves, bundle branch block, depressed S-T segments, prolonged conduction time and asystole, arrhythmias, heart block, fibrillation, myocardial infarction, stroke, and unexpected death in patients with cardiovascular disorders.

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

Allergic or Toxic
Skin rash, edema, pruritus, photosensitivity, obstructive jaundice and bone marrow depression, including agranulocytosis, leukopenia, eosinophilia, purpura and thrombocytopenia.

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

Miscellaneous

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 arrythmias 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 RHOTRIMINE. In cases 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 cathterization should be performed in the unconscious patient.

ECG monitoring in an intensive care unit is recommended in all patients, particularly in the presence of ECG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal. Because of its effects 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 CNS anticholinergic manifestation 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 RHOTRIMINE (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 to150 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, RHOTRIMINE may be administered in a single dose before bedtime, provided such a dosage regimen is well tolerated.

AVAILABILITY

Tablets:

12.5 mg: Each round, coated, dark pink tablet contains: trimipramine 12.5 mg. One side of the tablet is plain and the other side contains the logo “RH”. Bottles of 500.

25 mg: Each round, coated, dark pink tablet contains: trimipramine 25 mg. The tablet is plain on one side and identified “25" on the other. Bottles of 100 and 500.

50 mg: Each round, coated, dark pink tablet contains: trimipramine 50 mg. The tablet is plain on one side and identified “50" on the other. Bottles of 500.

100 mg: Each round, coated, dark pink tablet contains: trimipramine 100 mg. The tablet is plain on one side and identified “100" on the other. Bottles of 100.

Capsules: Each opaque, gelatin No. 1 capsule with pink cap and chamois body contains: trimipramine 75 mg. Bottles of 500.

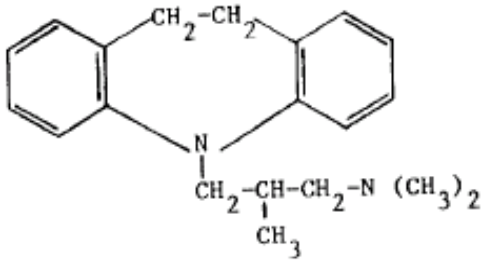
Non-medicinal ingredients:

Tablets: acetic anhyride, cellulose, colloidal silicon dioxide, diethyl phthalate, erythrosine, FD&C Red No. 3, lactose, magnesium stearate, sodium croscarmellose, talc, titanium dioxide and zein. Tartrazine-free.

Capsules: calcium phosphate dibasic, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 3, gelatin, magnesium stearate, polacrillin potassium and titanium oxide. Tartrazine-free.

CHEMISTRY AND PHARMACOLOGY

Trimipramine is 5-3-(2-methyl)dimethylaminopropyl iminodibenzyl and has the following structural formula:



As with other tricyclic antidepressants trimipramine antagonizes reserpine-induced depression and post-electroshock depression in the rabbit and in the rat. It also potentiates the narcotic effect of ether and hexobarbital and depresses spontaneous activity in mice, but has no cataleptic action and does not significantly block conditioned reflex responses.

RHOTRIMINE has anti-convulsive action against maximal electroshock and a pro-convulsant effect on metrazol-induced convulsions and displays *in vitro* antiserotonin and antihistaminic activity. It has also antiemetic and analgesic properties.

Like other tricyclic drugs, trimipramine potentiates the pressor effect of norepinephrine but reduces or reverses the pressor effect of epinephrine, and has anticholinergic properties.

It has a transient lowering effect on the blood pressure when injected intravenously and induces tachycardia of short duration. As other tricyclic agents, in the chloralosed-anesthetized dog, subtoxic dosage levels depress conduction in the heart muscle and broaden the QRS complex giving the picture of a quinidine-like effect.

TOXICOLOGY

Acute toxicity

The LD_{50} in the mouse is 58 mg/kg I.V., 200 mg/kg S.C. and 250 mg/kg P.O.

At toxic doses, the animals developed sporadic convulsions and depression; they died from respiratory arrest during a final convulsive attack. At subtoxic dosages, mice did not present definite spontaneous psychomotor hyperactivity, but they responded strongly to a variety of stimuli (auditory and mechanical).

In the rat, the LD_{50} is1140 mg/kg P.O.

In the dog, single doses as high as 2000 mg/kg failed to produce death. This may be due to either the low toxicity of the drug or a loss of dose by emesis. At all doses levels these animals showed decreased activity, dyspnea and prostration.

Sub-acute toxicity

Sub-acute studies in rats at oral dosages of 0, 20 and 40 mg/kg and in dogs at 0, 15 and 30 mg/kg did not influence the weight curve of the treated groups of animals. Hematological tests before, during and after treatment yielded normal results in the rat, while in the dog signs of anemia became evident at the end of treatment. A slight increase in urinary bile salts and occasionally in urobilin levels was noted, but there was no damage to the liver tissue.

Chronic toxicity

A chronic toxicity study using daily oral doses of 6.67, 20 and 60 mg/kg of RHOTRIMINE 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 behavior. 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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