Surmontil®
(trimipramine maleate)

DESCRIPTION
Surmontil (trimipramine maleate) is 5-[3-dimethylamino-2-methy(propyl)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (racemic form).

Molecular Formula: C25H27ClN2O·H2C03
Molecular Weight: 410.5

Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow 10 and FD&C Yellow 6; the 50 mg dosage strength also contains D&C Red 28, FD&C Red 40, and FD&C Yellow 6.

Trimipramine maleate is prepared as a racemic mixture which can be resolved into levorotatory and dextrorotatory isomers. The asymmetric center responsible for optical isomerism is marked in the formula by an asterisk. Trimipramine maleate is an almost odorless, white or slightly cream-colored, crystalline substance, melting at 140°-144° C. It is very slightly soluble in ether and water, is slightly soluble in ethanol and acetone, and freely soluble in chloroform and methanol at 20° C.

CLINICAL PHARMACOLOGY
Surmontil is an antidepressant with an anxiety-reducing sedative component to its action. The mode of action of Surmontil on the central nervous system is not known. However, unlike amphetamine-type compounds it does not act primarily by stimulation of the central nervous system. It does not act by inhibition of the monoamine oxidase system.

INDICATIONS AND USAGE
Surmontil is indicated for the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states, in studies with neurotic outpatients, the drug appeared to be somewhat less effective than other antidepressants.

CONTRAINDICATIONS
Surmontil should not be administered to patients suffering from any of the contraindications listed below because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold, patients receiving guanethidine or similar agents, since Surmontil may block the pharmacologic effects of these drugs. Since the drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

PRECAUTIONS
General
The possibility of suicide is inherent in any severely depressed patient and persists until a significant remission occurs. When a patient with a serious suicidal potential is not hospitalized, the prescription should be for the smallest amount feasible.

In schizophrenic patients activation of the psychosis may occur and require reduction of dosage or the addition of a major tranquilizer to the therapeutic regime.

MANO: Hyperpyrexia and convulsive crises, transient increases in blood pressure, tachycardia, myocardial infarction, strokes, and narrow-angle glaucoma because of the drug's effects on adrenergic properties; hypertension or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

WARNINGS
General Consideration for Use
Surmontil should be used when this drug is given to patients with any evidence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

Concomitant use of monoamine oxidase inhibitors (MAO) and tricyclic compounds similar to Surmontil has caused severe hypertensive reactions, convulsive crises, and death in some patients. At least two weeks should elapse after cessation of therapy with MAO inhibitors before instituting therapy with Surmontil. It is desirable to reduce the dosage should be low and increased gradually with caution and careful observation of the patient. The drug is contraindicated during the acute recovery period after a myocardial infarction.

Drug Interactions
Cimetidine
There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of Surmontil dosage may be required if cimetidine therapy is initiated; upward adjustment if cimetidine therapy is discontinued.

Alcohol
Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggeration of effects.

Catecholamines/Anticholinergics
It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, antiparkinson effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing ephedrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day should be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

Dugs Metabolized by P450 2D6
The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylation) is reduced in a subset of the caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"). Reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fractional clearance of the digitized drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of the isozyme and make normal metabolism resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antihistaminic propionate and fexofenidine). 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. The extent to which SSR TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSR involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA therapy in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whatever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Severe studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional occurrence of hepatic congestion, fatty infiltration, or increased serum liver enzymes at the highest dose of 60 mg/kg/day.

Both elevation and lowering of blood sugar have been reported with tricyclic antidepressants.

Teratogenic Effects—Pregnancy Category C
Surmontil has shown evidence of embryotoxicity and/or increased incidence...
**ADVERSE REACTIONS**

Note: The pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when Surmontil is administered. Some of the adverse reactions included in this list are not in fact reported with Surmontil.

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

**Psychiatric**
- Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hyperactivity; exacerbation of psychosis.
- Numbness, tingling, paresthesias of extremities; incoordination, ataxia, transient dystonic reactions (torticollis, pseudobulbar palsy, dystonia); mental confusion, delirium, disorientation; mania.

**Neurologic**
- Numbness and tingling, paresthesias of extremities; blurred vision, disturbances of accommodation, mydriasis, constipation, dry mouth, urinary incontinence, retention, delayed micturition, dilution of the urinary tract.

**Allergic**
- Skin rash, pruritis, urticaria, itching, photosensitization, edema of face and tongue.

**Hematologic**
- Depression of blood-sugar levels.

**Gastrointestinal**
- Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

**Endocrine**
- Dry mouth and, rarely, associated sublingual adenitis; blurring vision, disturbances of accommodation, mydriasis, constipation, dry mouth, urinary incontinence, retention, delayed micturition, dilution of the urinary tract.

**Other**
- Jaundice (simulating obstructive); altered liver function; weight gain or loss; changes in hair, skin, and nail color; pruritis; urticaria, flushing, skin rash, petechiae, urticaria, itching, photosensitization, edema of face and tongue.

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

**DOSAGE AND ADMINISTRATION**

Dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance.

**Dosage**
- Initially, 100 mg/day in divided doses. This may be increased to the maximum recommended dose of 250 to 300 mg/day, depending upon individual response and tolerance. If improvement does not occur in 2 to 3 weeks, the dose may be increased to the maximum recommended dose of 250 to 300 mg/day.

**Adolescent and Geriatric Patients** — Initially, a dose of 50 mg/day is recommended, with gradual increments up to 100 mg/day, depending upon patient response and tolerance.

**Maintenance** — Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission. Maintenance therapy is preferably administered as a single dose at bedtime. To minimize relapse, maintenance therapy should be continued for about three months.

**OVERTOXICITY**

Deaths may occur from overdose 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 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 overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis and width, are clinically significant indicators of tricyclic antidepressant toxicity.

**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. Plasma drug levels may not reflect the severity of the poisoning. Therefore, monitoring of plasma drug levels alone should not guide management of the patient.

**Gastrointestinal Decomantation**
- All patients suspected of 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 tox-lead QRS duration of ≥0.10 seconds has been associated with an increased incidence of seizures. A QRS duration of > 0.16 seconds has been associated with an increased incidence of ventricular dysrhythmias. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.50. 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 mm Hg 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, procainamide).

**Other**
- In rare instances, hemopoesis may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have all been reported as ineffective in tricyclic antidepressant poisoning.

**CNS**
- Patients with CNS depression, early intubation is advisable 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 consultation with a poison control center.

**Psychiatric Follow-up**
- Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase.

**Management**
- The principles of management of child and adult overdoses are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

**HOW SUPPLIED**

Surmontil® (trimipramine maleate) Capsules are available in the following dosage strengths:
- 25 mg, NDC 0008-4132, opaque blue and white capsule marked “WYETH” and “4132”, in bottles of 100 capsules.
- 50 mg, NDC 0008-4133, opaque blue and orange capsule marked “WYETH” and “4132”, in bottles of 100 capsules.
- 100 mg, NDC 0008-4158, opaque blue and white capsule marked “WYETH” and “4158”, in bottles of 100 capsules.

Store at room temperature, approximately 25°C (77°F).

**Keep bottles tightly closed.**

**Dispense in a tight container.**

**Protect capsules packaged in blister strips from moisture.**

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories, by arrangement with Rhone-Poulenc Rorer France.

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