NAME OF THE MEDICINE

SURMONTIL tablets and capsules contain trimipramine (as maleate).

The chemical name for trimipramine maleate is (2RS)-3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-N,N,2-trimethylpropan-1-amine (Z)-butenedioate. (CAS No.: 521-78-8) and the chemical structure is:

\[
\text{C}_{20}\text{H}_{26}\text{N}_2\text{C}_4\text{H}_4\text{O}_4, \text{ molecular weight is 410.5.}
\]

DESCRIPTION

Trimipramine maleate is a white or almost white, crystalline powder. It is slightly soluble in water and in ethanol (96%).

SURMONTIL tablets contain 25 mg trimipramine. They also contain the excipients calcium hydrogen phosphate, dextrin, indigo carmine, kaolin, magnesium stearate, sodium lauryl sulfate and starch-wheat.

SURMONTIL capsules contain 50 mg trimipramine. They also contain the excipients cellulose-microcrystalline, gelatin, indigo carmine, iron oxide yellow, magnesium stearate, opacode S-1-8152 HV Black (PI), silica-colloidal anhydrous, starch-maize and titanium dioxide.

ACTIONS

The anxiolytic action produces restoration of normal sleep patterns and a subjective improvement in the patients. The antidepressant action produces mood elevation, usually within 7 to 10 days.

PHARMACOKINETICS

Trimipramine is metabolised in the liver to its major metabolite desmethyltrimipramine. Trimipramine is excreted in the urine, mainly in the form of its metabolites, and has been shown to have a mean elimination half life of 24 hours after a 50mg oral dose. Trimipramine has been shown to be extensively bound to plasma proteins (average of 94.9%) and it has been suggested that it undergoes high first-pass hepatic clearance.
INDICATIONS

For the treatment of major depression.

The 50 mg capsule is indicated for the maintenance treatment of major depression (See Precautions).

CONTRAINDICATIONS

Recent myocardial infarction. Any degree of heart block or other cardiac arrhythmia. Mania, severe liver disease.

PRECAUTIONS

MAOIs should be withdrawn at least 2 weeks before Surmontil treatment is started. Surmontil enhances the actions of anaesthetics, sedatives, alcohol, narcotics, hypotensive agents and sympathomimetic drugs, including amphetamines.

Certain activities, such as the control of vehicles and machinery, should not be undertaken until any sedative effect has subsided.

Particular care must be taken in the treatment of patients suffering from alcoholism, pre-existing hepatic disease, epilepsy, brain damage, glaucoma, hyperthyroidism and in those predisposed to mood reversal. Treatment should be avoided, if possible, in patients with symptoms suggestive of prostatic hypertrophy. It must be remembered that the risk of suicide is greatest when the patient begins to respond to medications.

Clinical worsening and suicide risk associated with psychiatric disorders

The risk of suicide attempts is inherent in depression and may persist until significant remission occurs. The 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 behaviours (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 dose 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 patients’ 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/behaviours or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analysis of 24 short-term (4-16 weeks) placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There
was considerable variation in risk among the antidepressants but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from the trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Pooled analysis of short term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months). Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

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 non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression ans/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 any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour 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 Surmontil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

**Use in Children and Adolescents (<18 years)**
The safety and efficacy of Surmontil for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Surmontil should not be used in this age group for the treatment of depression or other psychiatric disorders.

**Surmontil 50 mg Capsules**
Surmontil 50 mg capsules are indicated only for the maintenance treatment of major depression. The 50 mg capsules should not be used in acutely ill patients where there is a risk of suicide. There is an increased risk of completed suicide by overdose with 50 mg capsule compared with the 25 mg tablet.

**Use in Pregnancy:** (Category C - Drugs which, owing to their pharmacological effects, have caused, or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.)

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 trimipramine 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.

**Use in Lactation**
Safety in lactation has not been established.

**Interactions with other medicines**
A potentially lethal interaction can occur between tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) - see PRECAUTIONS.

As with other tricyclic antidepressants, Surmontil may cause the effects of bethanidine, debrisoquine, guanethidine and possibly other antihypertensive agents to be attenuated and may give rise to hypertension in patients given local anaesthetics containing adrenaline or noradrenaline.

**ADVERSE EFFECTS**
Side effects are similar to those of other tricyclic antidepressants and are usually more evident during the first few days of treatment. They invariably respond to modification of dosage. An initial day time drowsiness may occur, but this is minimised by giving the total daily dosage at night. Other effects include vertigo, hypotension, tachycardia, paraesthesia, gastrointestinal upsets, headaches, and atropine-like side effects. Confusion may occur in elderly, alcoholic or arteriosclerotic patients. Insomnia and reversal of sleep rhythm have been reported. At high dosage levels, mood swing to a mild hypomania has occurred and, rarely, extrapyramidal side effects and epileptiform seizures.

**DOSAGE AND ADMINISTRATION**

**Use in Children and Adolescents (<18 years)**
The safety and efficacy of Surmontil for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Surmontil should not be used in this age group for the treatment of depression or other psychiatric disorders (refer to PRECAUTIONS).

**Mild/moderate depression.** (In general practice). Recommended dosage is 50 to 100 mg orally, given two hours before bedtime, larger doses (75 to 100 mg) being preferable for those patients with more marked sleep disturbance. Giving the total daily requirement at night induces a rapid return to normal sleep and minimises daytime drowsiness. Treatment should be continued for at least three weeks.

**Moderate/severe depression** (hospitalised patients). Initial dosage: 75 mg/day orally. This may be given as a single dose late in the evening, or 25 mg at midday and 50 mg late in the evening. Daily increments are of 25 mg until the optimum therapeutic dosage is reached, usually 150 to 300 mg/day. Treatment at this dosage should be continued for four to six weeks, dosage then being reduced to a maintenance level, usually within the range of 75 to 150 mg/day, for two to three months. Giving most of the total dosage at night induces a rapid return to normal sleep, reduces the need for night sedation and minimises daytime drowsiness.

**OVERDOSAGE**

**Symptoms.** Acute overdosage may be accompanied by hypotensive collapse, convulsions and coma.

**Treatment.** Provided coma is not present, gastric lavage should be carried out without delay even if some time has elapsed since the drug was ingested. Patients in coma should have an endotrachial tube passed before gastric lavage is started.
Absorption is slow, but as cardiac effects may appear soon after absorption, a saline purge should be given in conjunction with the gastric lavage. ECG monitoring is essential. It is important to treat acidosis as it appears. Convulsions should be treated with intravenous diazepam. Ventricular tachycardia or fibrillation should be treated by electrical defibrillation. Treatment should be continued for at least 3 days even if the patient appears to have recovered.

Physostigmine may be used to control adverse cardiovascular effects of acute tricyclic poisoning. Due to serious or fatal reactions to physostigmine, its use should be supervised by physicians with adequate expertise.

In adults, physostigmine can be given as a slow intravenous injection at a rate no greater than 1mg/minute. An initial dose of 0.5mg to 2mg may be given by slow intravenous injection repeated hourly or two hourly as necessary.

In children an initial dose of not more than 0.5mg by slow intravenous injection over at least one minute may be given. If toxic effects persist and there is no sign of cholinergic effects, repeat the dose at five to ten minute intervals until the desired therapeutic effect is reached or a maximum of 2mg total dose has been used.

Care must be taken, to avoid physostigmine induced convulsions which occur after rapid intravenous administration, and also should be taken in asthmatic patients. The use of neostigmine has also been suggested.

PRESENTATION AND STORAGE CONDITIONS

Tablets, 25 mg: Pale blue, thin, circular tablet. Packs of 50 tablets.

Capsules, 50 mg: Hard gelatin capsule with a white body and green cap, “SU50” is printed longitudinally in black. Capsules contain a white to almost white powder. Packs of 50 capsules.

Storage
Store below 25°C. Protect from light.

POISON SCHEDULE
S4

NAME AND ADDRESS OF SPONSOR
Aspen Pharmacare Australia Pty Ltd
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AUSTRALIA

DATE OF APPROVAL
Approved by the TGA on 27 February 2004
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