1. NAME OF THE MEDICINAL PRODUCT

SURMONTIL 25mg

2. ACTIVE INGREDIENT

Trimipramine (as Maleate) 25 mg per tablet

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antidepressant

4.2 Posology and method of administration

Dosage:

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

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. It is not possible to prescribe a single dosage schedule of Surmontil that will be therapeutically effective in all patients. The physical psychodynamic factors contributing to depressive symptomatology are very complex; spontaneous remissions or exacerbations of depressive symptoms may occur with or without drug therapy. Consequently, the recommended dosage regimens are furnished as a guide which may be modified by factors such as the age of the patient, chronicity and severity of the disease, medical condition of the patient, and degree of psychotherapeutic support.

Most antidepressant drugs have a lag period of ten days to four weeks before a therapeutic response is noted. Increasing the dose will not shorten this period but rather increase the incidence of adverse reactions.

Usual Adult Dose
Outpatients and Office Patients --Initially, 75 mg/day in divided doses, increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance therapy is in the range of 50 to 150 mg/day. For convenient therapy and to facilitate patient compliance, the total dosage requirement may be given at bedtime.
Hospitalized Patients --Initially, 100 mg/day in divided doses. This may be increased gradually in a few days to 200 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.

Method of administration:

The pharmacokinetic characteristics of this medication render it suitable for a single daily dosing, during or between meals.
The medication may be administered in the evening to facilitate sleep.

Treatment duration:

The administration of an antidepressant corresponds to symptomatic treatment.
An episode of depression requires several months (generally about 6 months) of treatment to avoid relapse of the depression.

Concomitant psychotropes:
Combination with a sedative or anti-anxiety drug may prove useful at the start of the treatment to counter the onset or exacerbation of anxiety. However, anti-anxiety drugs do not necessarily provide protection against disinhibition.

High-risk populations
The elderly:
Start the treatment at a low dose, i.e. in practice half the lowest recommended dose (see 5.2 Pharmacokinetic properties).
If the dose needs to be increased, this should take place gradually under clinical supervision since the adverse effects exerted by imipramines may have serious consequences in the elderly (falls, confusion).

Liver and kidney impairment:
Reduce the dose (see 5.2 Pharmacokinetic properties).

4.3 Contra-indication

This medication SHOULD NEVER BE prescribed in the following cases:

-Hypersensitivity to the active substance trimipramine or to any of the excipients.

-Known risk of angle-closure glaucoma.
-Possible urinary retention due to urethra/prostate disorders.
-Recent myocardial infarction.

-Combination with sultopride (see interactions with other medicaments).
-Hypersensitivity or intolerance to gluten because of the presence of wheat starch (gluten),
The concomitant use of monoamine oxidase inhibitors (MAOI) and tricyclic compounds similar to Surmontil has caused severe hyperpyretic reactions, convulsive crises, and death in some patients. At least two weeks should elapse after cessation of therapy with MAOI before instituting therapy with Surmontil. Initial 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.

IT IS GENERALLY INADVISABLE to prescribe this medication in the following situations :

-Combination with alcohol, clonidine or analogues, alpha and beta sympathomimetics (adrenaline, noradrenaline, dopamine for systemic action by parenteral route) (see Interactions with other medicaments).

4.4 Special warnings and special precautions for use

Warnings

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide - related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide - related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo- controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion and postural hypotension.

Since rare cases of withdrawal effects (headaches, malaise, nausea, anxiety, sleep disorders) have been observed on treatment discontinuation, it is recommended to reduce the dose gradually and monitor the patient particularly carefully during this period.

Hyperglycemia/Diabetes:
Epidemiologic studies have identified an increased risk of diabetes mellitus in depressed patients receiving tricyclic antidepressants.
Therefore, patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on trimipramine, should get appropriate glycaemic monitoring (see section 4.8).

Serotonin syndrome
Serotonin syndrome may occur when tricyclic antidepressants are used concomitantly with other serotonergic active substances (see section 4.5).
Serotonin Syndrome which is caused by an excess in serotonin, may be fatal and includes the following symptoms:
• Neuromuscular excitation (clonus, hyperreflexia, myoclonus, rigidity),
• Autonomic changes (hyperthermia, tachycardia, changes in blood pressure, diaphoresis, tremor, flushing, dilated pupils, diarrhea),
• Changed mental state (anxiety, agitation, confusion, coma).
Close clinical monitoring is required when serotonergic active substances are combined with trimipramine. Treatment with trimipramine should be discontinued if serotonin syndrome occurs.

QT interval prolongation:
Like other tricyclic antidepressants, trimipramine may dose-dependently prolong QT interval (see section 4.8).
Caution should be taken in patients with known risk factors for prolongation of QT interval such as:
- congenital long QT syndrome, bradycardia
- concomitant use of drugs that are known to prolong the QT interval, induce bradycardia or hypokalemia (see section 4.5)
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia).

Special precautions for use

Insomnia or nervousness at the start of the treatment may require a dosage reduction or short-term symptomatic treatment.

If the patient shows a clear manic swing, discontinue the trimipramine treatment and generally prescribe a sedative neuroleptic.

In epileptics or those with a history of epilepsy it is prudent to reinforce clinical and EEG monitoring because of the possible reduction in the seizure threshold.
Stop the treatment if seizures occur.

Trimipramine should be used with caution:
- in elderly subjects presenting with:
- enhanced sensitivity to postural hypotension and sedation.
-chronic constipation (possible induction of paralytic ileus)
-possible prostate hypertrophy;
-in subjects suffering from certain cardiovascular disorders because of the quinidine-like, tachycardiac and hypertensive effects exerted by the members of this drug category;

- in patients with liver and kidney impairment because of possible overdosing (see 5.2 Pharmacokinetic properties).

Caution is advised in patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients receiving guanethidine or similar agents, since Surmontil (trimipramine maleate) 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.

4.5 Interactions with other medicaments and other forms of interaction

Combination with non-selective MAO inhibitors is a classic contra-indications for all imipramines because of the major (though infrequently documented) risk of hypotensive or hypertensive modifications.

CONTRA-INDICATED COMBINATIONS

+ Sultopride:
Enhanced risk of ventricular rhythm disorders, notably torsades de pointes by addition of the electrophysiological effects.

INADVISABLE COMBINATIONS

+ Alcohol:
Alcohol enhances the sedative effects of these substances. Decreased alerthness may render driving and the use of machines dangerous.
Avoid alcoholic beverages and alcohol-containing medications.

+ Clonidine and analogues:
Describe for desipramine and imipramine.
Inhibition of the antihypertensive effect of clonidine (antagonism at the Adrenergic receptors).

+ Alpha and beta sympathomimetics: adrenaline, noradrenaline, dopamine by parenteral route for systematic action.
Paroxystic hypertension with possible rhythm disorders (inhibition of adrenaline or noradrenaline penetration into the sympathetic fibre).

COMBINATIONS REQUIRING PRECATIONS FOR USE

+ Anticonvulsants:
Possible generalized seizures (the antidepressant lowers the seizure threshold) Clinical monitoring and possible dose adjustment.

- **Valproic acid, valpromide:**

Clinical monitoring and possible adjustment of the antidepressant dose.

- **Carbamazepine:**

Possible generalized seizures (the antidepressant lowers the seizure threshold), and reduced plasma concentrations of the antidepressant (increase in its hepatic metabolism induced by the andticonvulsant).
Clinical monitoring and possible dose adjustment.

+ Selective serotoninergic antidepressants:
citalopram, fluxetine, fluvoxamine, paroxetine, sertraline.
Increased plasma concentrations of both antidepressants with risk of seizures and enhanced undesirable effects.
If the two are combined, clinical monitoring should be intensified and the doses should be adjusted if necessary in the event that fluoxetine is replaced by an imipramine antidepressant, the latter should be started at a low dose which is gradually increased to take account of the long half-life of fluoxetine and its active metabolite).

+Co-administration with other serotonergic active substances (such as SSRIs, SNRIs, MAOIs, lithium, triptans, tramadol, linezolid, L-tryptophan, and St. John's Wort – Hypericum perforatum – preparations) **may lead to serotonin syndrome** (see section 4.4 Warnings and Special Precautions for Use). Close clinical monitoring is required when these substances are co-administered with trimipramine.

+ **Alpha and beta sympathomimetic:**
Adrenaline by sub-cutaneous gingival injection for local haemostatic effects.
Paroxystic hypertension with possible rhythm disorders (inhibiton of adrenaline or noradrenaline penetration into the sympathetic fibre)
Restrict the supply, e.g. less than 0.1 mg of adrenaline in 10 minutes or 0.3 mg in one hour in adults.

+Trimipramine should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III antiarrhythmics, macrolides, fluoroquinolones, some antifungals, some antipsychotics), induce hypokalemia (e.g. hypokalemic diuretics, stimulant laxatives, glucocorticoids, tetracosactides) or bradycardia (e.g. beta-blockers, diltiazem, verapamil, clonidine, digitalics) (see section 4.4 Warnings and Special Precautions for Use).
<u>COMBINATIONS TO BE TAKEN INTO ACCOUNT</u>

+ Antihypertensives (except clonidine and analogues):
Antihypertensive effect and enhanced risk of postural hypotension (additive effects).
(clonidine and analogues: see inadvisable combinations).

+ Atropine and atropine-like substances:
Sedative H_1 antihistamines, anticholinergic antiparkinsonians, atropine-like antispasmodics, disopyramide, phenothiazine neuroleptics.
Addition of atropine-related undesirable effects such as urinary retention, constipation, dry mouth etc.

+ Other central nervous system (CNS) depressants:

Morphine derivatives (analgesics, antitussives and replacement therapies) ;
barbiturates benzodiazepines; anti-anxiety drugs other than benzodiazepines:
carbamates, captodiame, etifoxine; hypnotics; neuroleptics; sedative H1 antihistamines; central antihypertensives; baclofen; thalidomide.

Enhanced central depression. The resulting decrease in alertness may render driving and the use of machines dangerous.

+ Baclofen:
Possible increase in muscle hypotonia.

+ Guanethidine: (see ocular)
Described for amitryptiline desipramine, imipramine and maprotiline.
Reduced antihyperiensive effect of guanethidine (inhibition of its penetration into the sympathetic fibre, its site of action).

4.6 Pregnancy and lactation

Pregnancy:
Surmontil has shown evidence of embryotoxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in pregnant women. Surmontil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation:
Little is known as regards secretion into maternal milk, but the amount concerned are probably small. Nevertheless, as a precautionary measure, breast-feeding should be avoided during the treatment period.

4.7 Effects on the ability to drive and use machines

This medication may diminish the mental and physical faculties required to perform certain hazardous tasks such as operating machinery or driving motorised vehicles.

4.8 Undesirable effects

The undesirable effects of trimipramine are related, for the most part, to the pharmacological properties of imipramine antidepressants.

Cardiovascular
Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.
QT interval prolongation, torsade de pointes (see section 4.4).

The following are peripherally-mediated effects; they are usually benign and most often resolve in the course of treatment or after dose reduction:

- Anticholinergic effects (in decreasing order of frequency): dry mouth, constipation, difficulty focusing, tachycardia, sweating, urination difficulties and possibly urinary retention; blurred vision.
- Adrenolytic effects: postural hypotension, impotence.

The following are centrally-mediated effects:

- frequent : drowsiness or sedation (antihistamine effect), more pronounced at the beginning of treatment;
- much rarer: tremor, seizures in predisposed patients, transient confusional state.

The following effects are related to the depressive condition itself:

- suppression of psychomotor inhibition, with a risk of suicide;
- mood swings with manic episodes;
- recurrence of delusions in psychotic patients.

Cases of suicidal ideation and behavior have been reported during or shortly after treatment with Surmontil or shortly after treatment discontinuation (see Section 4.4.).

Imipramine antidepressants may also cause:
- weight gain,
- conduction disorders or arrhythmias (at high doses),
- endocrine disorders; enlargement of the breast, galactorrhoea,
- hot flushes,
- allergic skin reactions,
- dysarthria,
- rare cases of cytolytic or cholestatic hepatitis
- haematlogical disorders: hypereosinophilia, leukopenia, agranulocytosis, thrombocytopenia,
- syncope.

Prevention or treatment of some of these undesirable effects is possible using adjuvant or corrective therapy, or even dose reduction

Epidemiological studies, conducted primarily in patients aged 50 years and over, have shown an increased risk of bone fracture in patients receiving selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants. This is caused by an unknown mechanism

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

Metabolism and nutrition disorders
Hyperglycemia. Epidemiologic studies have identified an increased risk
of diabetes mellitus in depressed patients receiving tricyclic

antidepressants (see section 4.4).

4.9 Overdose

Deliberate or accidental overdosing results in severe cardiovascular symptom (primarily conduction disorders (QT interval prolongation, torsade de pointe) that determine the gravity of the poisoning), exacerbated anticholinergic symptom, and possibly convulsions, confusion or coma (the ones of which may be delayed). In such cases, the patient should be immediately admitted to hospital in a specialized ward and the ingested product should be evacuated.
Overdose may result in fatal outcome.
The management procedure must include symptomatic treatment and monitoring of vital function, particularly cardiac and respiratory functions, for at least five days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ANTIDEPRESSANT/NON-SELECTIVE MONOAMINE UPTAKE INHIBITOR
(N: nervous system).
The biochemical action likely to be responsible for the therapeutic effect are based on reduced presynaptic uptake of noradrenaline. Its synaptic transmission is therefore facilitated.
The sedative effect is related to the histaminergic component of the drug.
This part of the drug exerts central and peripheral anticholinergic effects that are responsible for adverse effects.
The adrenolytic properties of this drug may cause postural hypotension.
The improvement specifically in mood is often delayed in comparison with symptomatic improvements such as psychomotor retardation, insomnia or anxiety.
This notion must be taken into account before withdrawing the treatment for inefficacy, or when adjusting effective doses.

5.2 Pharmacokinetic properties

Absorption

Because of a very marked first pass effect through the liver, the bioavailability of trimipramine is lower after oral administration than after parenteral administration.

Distirbution

Trimipramine passes through the blood-brain barrier and into the placental and maternal milk.
Bingding to plasma proteins:
A high proportion of the drug is bound to proteins (95%).
Elimination half-life:
The plasma elimination half-life of trimipramine is approximately 24 hours.

Metabolism

The liver plays a major role in the metabolism of imipramine antidepressants:
uptake (first pass effect), then extensive biotransformation, explaining:
- the high plasma clearance value with respect to liver blood flow (1.5 l/min).
- the small percentage of active compounds found in the urine.

The principal metabolite of trimipramine is demethylimipramine, which is an active compound.

High-risk populations
-The elderly: the metabolic capacity of the liver is reduced, resulting in lower total clearance, higher steady-state concentrations and increased unbound fraction and half-life. The dose should therefore be reduced, at least at the start of the treatment.
- Liver and kidney impairment: the trimipramine dose should be reduced.

6. PHARMACEUTICAL PARTICULARS

Inactive ingredients: wheat starch, silica colloidal hydrated, magnesium stearate.

6.1 Special precautions for storage

Do not store above 25ºC.
Store the blisters in the outer packaging protected from light and humidity.

Manufacturer : Famar Lyon France
License Holder : Sanofi-aventis Israel ltd.

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