Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Surmontil 50mg hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Trimipramine Maleate equivalent to 50 mg of Trimipramine.

Excipients: each capsule contains soya lecithin (trace amounts)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule
Opaque, size 1 hard capsules with a white body and green cap that contains an off-white or slightly cream powder. "SU50" is printed in black longitudinally on both ends."

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Surmontil is indicated in the treatment of depressive illness, especially where sleep disturbance, anxiety, or agitation are presenting symptoms. Sleep disturbance is controlled within 24 hours and true antidepressant action follows within 7 to 10 days.

4.2 Posology and method of administration

The route of administration is oral.

Recommended Dosage:
Depression:
Adults:
The usual daily dose is 50 - 100 mg daily as a single dose, 2 hours before retiring.

In more severe depression, dosage should be increased gradually until the optimum therapeutic response is achieved (usually 150 - 300 mg daily) then reduced after 4-6 weeks to a maintenance level of 75 - 150 mg daily.

Elderly:
Initially, a low dosage is recommended, generally half the minimum recommended dose (see Pharmacokinetic Data). Increasing dosage, if required, must take place gradually under clinical supervision: the side effects of imipramines may have serious consequences in elderly patients (falls, confusion).

Paediatric Population:
Surmontil should not be used in the treatment of children or adolescents under the age of 18 years (see section 4.4 and 4.8).

Patients with hepatic or renal insufficiency:
In patients with hepatic and renal insufficiency a lower dosage is recommended (see section 5.2).

4.3 Contraindications

Trimipramine must not be used in the following cases:

- hypersensitivity to the active substance, other tricyclic antidepressants or to any of the excipients listed in section 6.1
- known risk of narrow angle glaucoma

- urinary disorders such as urinary retention or prostatic hyperplasia with formation of residual urine
- recent myocardial infarction
- any degree of heartblock or other cardiac arrhythmias
- mania.
- comedication with irreversible MAO inhibitors
- sultopride, see interactions selegiline, see interactions
- alcohol, clonidine and related compounds, alpha and beta sympathomimetics (epinephrine, norepinephrine, dopamine for systemic action by parenteral route; see interactions)

4.4 Special warnings and precautions for use

The drug should only be used with great caution in the elderly or the debilitated.

The drug should only be used with great caution in patients with a history of epilepsy or recent convulsions, urinary retention, glaucoma, hyperthyroidism, or cardiovascular disorders, particularly in patients with previous myocardial infarction or coronary insufficiency, blood dyscrasias, alcoholism, pre-existing brain damage, or in conjunction with electroconvulsive therapy.

Patients with severe depression should be kept under close surveillance, particularly during the early stages of treatment. Patients receiving anti-depressant therapy should be kept under regular surveillance and particular attention to effects on cerebral function, haemopoeitic function, myocardial conduction disorders.

Patients with cardiac disorders and elderly patients
Patients presenting certain cardiovascular disorders and elderly patients should be subject to regular cardiological assessments since this class of compound may increase the risk of tachycardia, hypotension and quinidine-like effects.
Trimipramine can cause hepatic adverse events (see Section 4.8) and is mainly metabolised by the liver. It should be used with great caution in patients with hepatic insufficiency. It may be advisable to monitor liver function in patients on long term treatment with surmontil because of the risk of overdosage (see section 5.2).

Discontinuation of Treatment
Cases of withdrawal syndrome (headaches, malaise, nausea, anxiety, restlessness, increased irritability, and sleep disorders) have been observed when treatment was discontinued. Therefore, it is recommended that the dose is gradually reduced and that the patient is monitored particularly closely during this period (see section 4.2).
Insomnia or nervousness at the start of treatment may require reduced doses or transient symptomatic treatment.

Manic episodes
In cases of sudden manic episodes, trimipramine treatment must be discontinued and suitable treatment instituted.

Seizures
For patients with epilepsy or a suspected epilepsy, increased clinical EEG monitoring is recommended due to the possibility of trimipramine lowering the seizure threshold (see section 4.5). The onset of seizures requires discontinuation of the treatment.

- Trimipramine should only be used with special caution in the following cases: In elderly patients more susceptible to postural hypotension and sedation, chronic constipation (risk of paralytic ileus) and possible prostatic hypertrophy;
- In patients presenting certain cardiovascular disorders since this class of compound may increase the risk of tachycardia, hypotension and quinidine-related effects;
- In patients with severe hepatic or renal insufficiency (see section 5.2).

Trimipramine should not be used in the treatment of children and adolescents under the age of 18 years. Studies in depression in this age group did not show beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants (selective serotonin reuptake inhibitors) have shown a risk of suicidality, self harm and hostility related to these compounds. This risk cannot be excluded with Trimpramine. Furthermore, long term safety data in children and adolescents concerning growth maturation and cognitive and behavioural development are not available (see also section 4.8 Undesirable effects and section 4.9 Overdose)

Suicidal thoughts/behaviour: 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 behaviour 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 behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms occur.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated.

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, a potentially life threatening condition, may occur when tricyclic antidepressants are used concomitantly with other serotonergic active substances/buprenorphine (see section 4.5). Serotonin Syndrome which is caused by an excess of serotonin, may be fatal and includes the following symptoms:

- Neuromuscular excitation (clonus, hyperreflexia, myoclonus, rigidity),
- Autonomic instability (hyperthermia, tachycardia, changes in blood pressure, diaphoresis, tremor, flushing, dilated pupils, diarrhea),
- Changed mental state (anxiety, agitation, confusion, coma).
- Gastrointestinal symptoms.

Close clinical monitoring is required when serotonergic active substances are combined with trimipramine, particularly during treatment initiation and dose increases. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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 Interactions)
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol and other CNS depressants
The effect of alcohol and the coadministration of other central nervous system (CNS) depressants, such as:

- morphine derivatives (analgesics, antitussives and replacement therapies);
- hypnotics (e.g. barbiturates, benzodiazepines),
- anxiolytics other than benzodiazepines,
- sedative antihistamines,
- neuroleptics,
- central antihypertensives,
- baclofen,
- thalidomide,
- can cause increased CNS depression.

Consuming alcoholic beverages and other medicinal products containing alcohol should be avoided.

Baclofen

Comedication with baclofen is associated with a risk of muscular hypotonia.

Anticholinergic substances

Simultaneous administration of other substances that also have anticholinergic effects like trimipramine may be expected to intensify undesired peripheral effects (e.g. the onset of urinary retention, an acute flare-up of glaucoma, constipation, dry mouth of atropine-like substances like ipratropium bromide, tiotropium bromide, trospium chloride, butylscopolamine) and central effects (especially delirium).

Sympathomimetics

The potency of sympathomimetic amines (epinephrine, norepinephrine, dopamine for systemic action by parenteral route) can be increased by concomitant administration of Trimipramine: paroxysmal hypertension, possibly with ventricular arrhythmias.

MAO inhibitors

MAO inhibitors of the irreversible inhibitor type should be discontinued at least 14 days before starting treatment with trimipramine. Additional administration of reversible MAO inhibitors is possible in individual cases for treatment refractory depressions, taking all necessary precautions and with slow dosage increase.

Serotonergic substances

Simultaneous or prior administration of serotonin reuptake inhibitors, such as citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline can lead to an increase in the plasma concentrations of both antidepressants due to substrate competition. Concomitant administration requires increased clinical supervision and if necessary a dose reduction of Surmontil or the serotonin reuptake inhibitor.

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. Close clinical monitoring is required when these substances are co-administered with trimipramine.

Antihypertensives

Trimipramine can weaken the potency of antihypertensives of the guanethidine and clonidine type with the risk of rebound hypertension in patients treated with clonidine.

The simultaneous use of antihypertensives (excluding clonidine and related compounds) can increase their antihypertensive effect and increase the risk of postural hypotension.

Substances prolonging QT interval

The concurrent administration of drugs that also prolong the QT interval (e.g. class IA or III antiarrhythmics, antibiotics, antimalarials, antihistamines, neuroleptics) which can lead to hypokalaemia (e.g. certain diuretics, glucocorticoids), or bradycardia (e.g. beta-blockers, diltiazem, verapamil, clonidine, digitalics) or inhibit the hepatic metabolism of trimipramine (e.g. irreversible MAO inhibitors, imidazole antimycotics) is to be avoided.

Antipsychotic medicines

Combination therapy with antipsychotics can lead to an increase in the plasma concentration of the tricyclic antidepressant.

Cimetidine

The plasma concentration of tricyclic antidepressants can also be increased by coexisting therapy with cimetidine.

Antiepileptic medicines

A dose adjustment of antiepileptics may also be necessary since trimipramine can lower the seizure threshold and an increased

seizure tendency is to be expected. These patients should be clinically monitored.

Patients treated with valproic acid are to be clinically supervised and, if required, the dosage of the tricyclic antidepressant is to be adjusted.

Carbamazepine: risk of generalised convulsive episodes (lowering of the convulsive threshold by the antidepressant) and decreased antidepressant plasma concentrations (increased hepatic metabolism of the antidepressant by the antiepileptic drug). Clinical supervision and if necessary, adjustment of dosages.

Contraindicated combinations:

- Sultopride: increased risk of ventricular arrhythmias, particularly torsades de pointes as a result of added electrophysiologicial effects.
- Selegiline: increased risk of serotonin syndrome.

Inadvisable combinations:

- Sulpiride: risk of QT prolongation.
- Haloperidol, Pimozide, Sertindole, Ziprasidone: increased risk of side effects on the heart.

Other combinations:

- Zopiclone: There is limited evidence that zopiclone may reduce the absorption or increase the elimination rate of trimipramine. These effects could decrease the antidepressant activity of trimipramine or related tricyclic antidepressant drugs, although the clinical evidence remains unclear.
- Buprenorphine/Serotonin syndrome: Trimipramine should be used cautiously when co-administered with buprenorphine, as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of trimipramine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Trimipramine is not recommended during pregnancy unless clearly necessary and only after careful consideration of the benefit/risk. Nevertheless, the maintenance of a good maternal mental balance throughout pregnancy is desirable. If a medicinal treatment is required to ensure this balance, it should be started or continued at an effective dose throughout the pregnancy and, if possible, as monotherapy.

In the neonates of mothers treated with tricyclic antidepressant at the end of pregnancy, adaptation difficulties and withdrawal symptoms can occur in the first week of life, which may include (hypotonia, irritability, tremors and even seizures, respiratory disorders (polypnoea, sudden cyanosis, and respiratory distress) and gastrointestinal disorders (difficulty initiating feeding, delay in the passage of meconium and abdominal distension).

Breast-feeding
There are no available data on the presence of trimipramine in human milk, milk production, or the effects on the breastfed infant. However, physico-chemical data suggest excretion of trimipramine in breast milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of trimipramine taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Trimipramine has moderate to major influence on the ability to drive and use machines.
Trimipramine can cause blurry vision and sedation. Even when used as prescribed, this product can affect the capacity to react to the extent that, for example, the ability to drive or use machines is impaired.

4.8 Undesirable effects

Anti-cholinergic effects, hypotension; particularly orthostatic hypotension, central nervous system irritability, gastrointestinal upset, including constipation, dryness of the mouth, accommodation difficulties, dysuria, micturition disorders and in some cases urinary retention, perspiration, erectile dysfunction.

Other infrequently reported side effects include vertigo, unsteadiness when standing, tachycardia, and transient confusional states.

Side effects related to the depression itself include, removal of psychomotor inhibition with suicidal risk; mood swings with episodes of mania and renewed delusions in psychotic patients.

Hypersensitivity reactions such as skin rash, allergic skin reactions, dermatitis, hyperhidrosis, hot flush, facial oedema, angioedema and less commonly anaphylactic reactions have been reported.

Hyperglycemia. Epidemiologic studies have identified an increased risk of diabetes mellitus in depressed patients receiving tricyclic antidepressants (see section 4.4).

QT interval prolongation, torsade de pointes (see section 4.5).

Blood disorders such as neutropenia, leucocytosis, leucopenia, thrombocytopenia, eosinophilia, hypereosinophilia and agranulocytosis have been observed.

Effects have been seen on liver function tests, (raised gamma GT, increased transaminases, bilirubinemia and increased alkaline phosphatases), with more infrequent reports of jaundice, cytolytic hepatitis, choleostatic hepatitis and hepatitic necrosis.

Cardiac toxicity has been observed with reports of chest pain, cardiac failure atrial fibrillation, conduction disorders and other arrhythmias.

Other neurological adverse effects include headache, peripheral neuropathy, tremor ataxia, convulsive seizures, other extrapyramidal symptoms including speech difficulties and tinnitus: confusion or delirium may also occur.

Endocrine effects include hypoglycaemia, disorders of sexual function, gynaecomastia, breast hypertrophy and galactorrhoea with one report of hypothyroidism. Alterations in blood have also been observed and rarely SIADH (syndrome of inadequate ADH secretion).
As with other tricyclic antidepressants: an increase in the prolactin level and Macromastia and/or galactorrhoea.

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRI's or TCA's. The mechanism leading to this risk is unknown.

Other side effects reported include pruritus, sweating, alopecia, syncope, weight gain, constipation and Stevens-Johnson syndrome.

Withdrawal symptoms including anxiety, restlessness, diarrhoea and hot and cold flushes have been reported on discontinuation of treatment.

Cases of suicidal ideation and suicidal behaviours have been reported during Surmontil therapy or early after treatment discontinuation (see section 4.4).

Especially at the start of treatment: tremor, drowsiness, dizziness, sedation (antihistamine effect) dysarthria, paraesthesias, polyneuropathies, convulsive seizures and extrapyramidal disorders such as akathisia, gait disturbances, dyskinesias.

Some of these undesirable effects can be prevented or counteracted using adjuvant or corrective treatment or by reducing dosage.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

a) Symptoms of intoxication

Convulsions.

QT interval prolongation, torsades de pointes.

Overdose may result in fatal outcome.

Symptoms of overdosage may include excitement, restlessness with marked antimuscarinic effect including dry mouth, dilated pupils tachycardia, urinary retention and intestinal stasis. Severe symptoms include hypotensive collapse, convulsions, unconsciousness, acidosis, respiratory and cardiac depression as well as life threatening arrhythmias.

b) Treatment of intoxication
Management should include symptomatic treatment and the monitoring of vital functions, especially cardiac and respiratory function, for at least three to five days.

Immediate administration of medicinal charcoal. Due to anticholinergic effects of trimipramine, its absorption may be slower and delayed. Therefore, administration of charcoal should be continued and repeated every 4 to 6 hours, Controlled ventilation and use of a cardiac pacemaker. As antidote, slow intravenous administration of physostigmine salicylate (Köhler) 2 mg (adults) and 0.5–1 mg (children). The injection can be repeated if there is a recurrence of the symptoms of intoxication.

Haemodialysis or haemoperfusion are ineffective because of the large volume of distribution, low plasma levels and pronounced plasma protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants/Non-selective monoamine reuptake inhibitors.

ATC code: N06AA06

Tripramine has a potent antidepressant action similar to that of other tricyclic antidepressants. It also possesses a pronounced sedative action. Trimipramine is a tricyclic antidepressant.

5.2 Pharmacokinetic properties

Trimipramine is readily absorbed after oral administration. It is strongly protein bound. It is metabolised in the liver to its metabolite dimethyltrimipramine. Trimipramine is excreted in the urine mainly in the form of its metabolites. It has a T½ of 10 - 25 hours.

Elderly patients: Hepatic metabolism decreases thus lowering total clearance. Steady state concentrations, the free fraction and the half lives are increased. It is important to reduce the dose, at least in the early stages of treatment.

Patients with hepatic or renal insufficiency: reduce the dose of trimipramine.

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Microcrystalline Cellulose (E460)

Anhydrous Colloidal Silica
Magnesium Stearate

Capsule Shell
Gelatin
Titanium Dioxide (E171)
Indigo Carmine (E132)
Iron oxide Yellow (E172)

Ink
Opacode – S/1/8100 Black:
Shellac
Soya Lecithin (E322)
Antifoam DC 1510
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Surmontil 50 mg capsules are marketed in blister packs which are enclosed in a cardboard carton. Blister packs consist of an opaque 250-micron plain, rigid uPVC blister coated with PVdC 40 g/m^2 with a 20 micron aluminium foil hard tempered and lacquered 6.8 gsm.

Pack sizes: Blister packs of 28

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Neuraxpharm Ireland Limited
4045 Kingswood Road
Citywest
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23229/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1978

Date of last renewal: 5th October 2010

10 DATE OF REVISION OF THE TEXT

September 2023