Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tranylcypromine 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains tranylcypromine sulfate equivalent to 10mg of tranylcypromine base.

Excipients with known effect
Each tablet contains:
Aspartame (E951) 0.73 mg
Sucrose 0.09 mg
Ponceau 4R lake (E124) 0.14 mg
Carmoisine lake (E122) 0.16 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablets

Red, round, biconvex coated tablets imprinted in black with TRN on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tranylcypromine is a non-hydrazine monoamine oxidase inhibitor for the treatment of symptoms of depressive illness especially where phobic symptoms are present or where treatment with other types of anti-depressants has failed. It is not recommended for mild depressive states resulting from temporary situational difficulties.

4.2 Posology and method of administration

Tranylcypromine 10mg tablets are for oral administration only.

Adults

Initially, 1 tablet morning and afternoon. If the response is not adequate after the first week add a further tablet at midday, and continue for at least a week. A dosage of 3 tablets a day should only be exceeded with caution. When a satisfactory response has been obtained, dosage may be reduced to maintenance level often of 1 tablet a day.

When given with a tranquillizer, the dosage of‘tranylcypromine’ is not affected when given concurrently with electroconvulsive therapy; the usual dosage is 1 tablet twice a day during the series and 1 tablet a day afterwards as maintenance therapy.

Elderly (over 65 years):

Use with great caution and at a lower dosage

Children:

Tranylcypromine is not indicated for children under 18 years of age.

Method of administration
The coated tablets should be taken with some liquid (preferably with half a glass to a full glass of water).

4.3 Contraindications

Do not give tranylcypromine until at least two weeks after stopping treatment with other MAOIs.

Allow 3 weeks to elapse after stopping tranylcypromine before starting clomipramine or imipramine.

Tranylcypromine should not be taken by patients suffering from porphyria.
Do not give tranylcypromine with indirectly acting sympathomimetic amines such as amphetamine, fenfluramine or similar anti-obesity agents, ephedrine or phenylpropalomine (certain cold cures may contain such agents) or with levodopa or dopamine, as severe hypertensive reactions may result; with pethidine and closely related narcotic analgesics, and nefopam, as potentiation may occur; with dextromethorphan as a similar reaction has been reported; with other MAO Inhibitors, as symptoms of overdosage are possible; or with buspirone, since increased blood pressure may occur.

Reports of hyperactivity, hypertonicity, hyperpyrexia, coma and death have been associated with the use of tranylcypromine in combination with tricyclic antidepressants; Tetracyclic antidepressants should also be avoided. The use of clomipramine in patients already on tranylcypromine may be particularly hazardous. Use of MAO inhibitors with or after fluvoxamine has been reported to produce a serotonin syndrome, sometimes fatal.

Do not use tranylcypromine in patients with actual or suspected cerebrovascular disease or severe cardiovascular disease; in those with actual or suspected phaeochromocytoma, or with hyperthyroidism; or in those with known liver

4.4 Special warnings and precautions for use

Use tranylcypromine with great caution in elderly patients; in those with cardiovascular disease in whom physical activity should be regulated, as the drug may suppress anginal pain; and in epileptic patients, as tranylcypromine has a variable effect on the convulsive threshold in animals. Tranylcypromine may aggravate some co-existing symptoms in depression such as anxiety and agitation. Tranylcypromine should preferably be withdrawn at least two weeks before elective surgery because of possible drug interaction.
Caution should be exercised in prescribing tranylcypromine for patients with a previous history of dependence on drugs or alcohol.

Tranylcypromine therapy should be withdrawn gradually.

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 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 present.

This product contains the following excipients which may cause reactions.

Aspartame, this contains a source of phenylalanine which may be harmful for people with phenylketonuria.
Sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.
Carmosine and Ponceau 4R may cause allergic reaction.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when giving tranylcypromine with the following: guanethidine, as its action may be antagonised; reserpine, as hyperactivity may occur; methyldopa, as central excitation may result; other hypotensive agents because of possible additive effects; oral hypoglycaemic agents or insulin, as their action may be potentiated; anticholinergic antiparkinsonism drugs, as potentiation has been reported, narcotic analgesics, except pethidine which is contra-indicated (see above), because of possible potentiation; and carbamazepine, which has similarities with tricyclic antidepressants.

Metrizamide should be avoided in patients on MAO Inhibitors since they may lower the seizure threshold.

Although MAO Inhibitors have been used therapeutically with L-tryptophan. A neuromotor syndrome has been reported with this combination.

Patients should be specifically asked if they taking any other medication because of the possibility of drug interactions. Exercise caution when giving tranylcypromine under following conditions:

- In combination with other monoamine oxidase inhibitors (MAOI). Avoid for at least 2 weeks after stopping previous MAOI (for e.g. furazolidone, isocarboxazid, pargyline HCl and procarbazine HCl) and then start at a reduced dose. Similarly, at least a week should elapse between the discontinuance of tranylcypromine and the administration of another MAOI, or the re-administration of tranylcypromine. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations.

- In combination with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline since CNS effects of SSRI may be potentiated. Serious and even fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation leading to delirium and coma) in patients receiving Fluoxetine in combination with a MAOI, and in patients who have recently discontinued Fluoxetine and are then started on a MAOI. There also have been cases presented with features resembling neuroleptic malignant syndrome. These drugs should not be given together or within 2 weeks of treatment with either drug. MAOIs should not be started until at least 5 weeks after starting Fluoxetine, since Fluoxetine and its major metabolite have very long elimination half-lives.

- In combination with tricyclic antidepressants, due to increased risk of hypertension and CNS excitation. After stopping tranylcypromine, do not start tricyclic related antidepressants (including amitriptyline, carbamazepine or trimipramine) for 2 weeks, also MAO inhibitors should not be started until at least 1-2 weeks (3 weeks in case of clomipramine or imipramine) after stopping tricyclic antidepressants.

- In combination with other antidepressants, due to increased risk of hypertension. At least 10 days should elapse between the discontinuation of MAOI and the start of Buspirone HCl.

- In combination with sympathomimetic drugs including amphetamine, ephedrine, phenylpropanolamine and over-the-counter cough & cold, hay fever or weight reducing preparations containing vasoconstrictors, guanethidine, methyldopa, dopamine, levodopa and reserpine due to the risk of hypertensive crisis, headache and related symptoms. MAOIs in combination with tryptophan have been reported to cause behavioural and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations and Babinski's signs.

- In combination with anticholinergic anti-parkinsonism drugs. Anti-parkinsonism drugs should be used with caution in patients receiving MAOIs.

- In combination with bupropion. The concurrent administration of bupropion and a MAOI is contraindicated. At least two weeks should elapse between discontinuation of a MAOI and initiation of treatment with bupropion HCl.

- Avoid concomitant use with opioid analgesics as possible CNS excitation or depression (hypertension or hypotension) may occur. Wait until two weeks after stopping MAOIs before starting treatment with opioid analgesics.

- In combination with antiepileptics, since MAOIs possibly antagonize anticonvulsant effects of antiepileptics (convulsive threshold lowered).

- In combination with antihistamines, since antimuscarinic and sedative effects of antihistamines are increased by MAOIs.

- Use of MAOIs may enhance the effects of barbiturates and possibly other hypnotics, hypoglycaemics, and possibly antimuscarinic agents.

- In surgery. Patients taking MAOIs should not undergo surgery requiring general anaesthesia. Also, they should not be given cocaine or local anaesthesia containing vasoconstrictors. The possible combined hypotensive effects of MAOIs and spinal anaesthesia should be kept in mind. Discontinue MAOI therapy two weeks before surgery because of the possible hazardous interaction with certain anaesthetics.

Dietary Precautions:

High levels of tyramine in certain foods have been the cause of severe hypertensive reactions in patients on MAO inhibitor therapy (See adverse reactions). Accordingly, patients must be warned to avoid the following: Matured cheeses, hydrolysed protein extracts such as Marmite or Bovril, alcoholic drinks, particularly red wines such as chianti, non-alcoholic beer and lager, and protein foods that are not fresh or whose preparation involved hydrolysis, fermentation, pickling or hanging, also broad bean pods which contain levodopa and banana skins.

4.6 Fertility, pregnancy and lactation

There are no data from the use of trancylcypromine in pregnant women. Animal studies are insufficient with respect to reproduction toxicity. Tranylcypromine should not be used in pregnancy, unless considered essential by the physician. T. The drug is excreted in human milk and has been also found to pass into the milk in lactating dogs. A risk to the suckling child cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from tranylcypromine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

No fertility data are available.

4.7 Effects on ability to drive and use machines

Tranylcypromine may affect the ability to drive and operate machinery. Patients should not undertake such activities unless it has been shown not to affect mental or physical capacity.

4.8 Undesirable effects

Insomnia is the most frequent side effect; it may usually be overcome by giving the last dose of the day not later than 3 p.m., by reducing dosage, or by prescribing a mild hypnotic.

Other undesirable effects include postural hypertension (which is usually temporary, but if it persists the drug should be stopped), dizziness, drowsiness, fatigue, dry mouth, blurred vision, headache, diarrhoea, nausea and vomiting, sleep disturbances, rash and rarely hepatocellular damage, jaundice, hallucinations and blood dyscrasias. Overstimulation including anxiety and agitation, developing rarely into hypomanias has also been observed.

Severe hypertensive reactions may occur, notably in association with foods containing tyramine (see section 4.5). On occasions these have been fatal. Symptoms may be pain and stiffness in the neck, multiple extrasystoles, often with substernal pain, sweating, and pallor, sometimes followed by flushing, mydriasis and photophobia.

Throbbing headache may be an early warning of hypertensive crisis.
Dependence on tranylcypromine with tolerance to high doses has been reported rarely and can occur in patients without past history of drug dependence. This should be distinguished from the return of features of the original illness on cessation of treatment.

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

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 the online reporting option (preferred method) accessible from the IMB homepage (www.imb.ie). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used. FREEPOST, Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: +353 1 6764971 Fax: +353 1 6762517 Website: http://www.imb.ie/ e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Signs and symptoms are usually of the type already described as adverse reactions, but may be more intense, may include hyperpyrexia, tremor and convulsions, and may follow a latent period. Treatment consists of the induction of vomiting and/or gastric lavage together with supportive and symptomatic measures. External cooling is recommended for hyperpyrexia. Treat hypotension with fluid replacement; if severe or persistent, noradrenaline may be considered. Hypertension, if it occurs, may be relieved by slow intravenous injection of phentolamine mesylate. Pancuronium with mechanical ventilation may help reverse muscle spasm and pyrexia. Beta-Adrenergic receptor blockade has been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N06AF04
Tranylcypromine is a non-Hydrazine monoamine oxidase inhibitor

5.2 Pharmacokinetic properties

Tranylcypromine is rapidly absorbed after oral administration. Peak plasma levels are reached after about 2.5 hours and the half-life is of the order of 2 hours. Excretion is pH dependent. Tranylcypromine undergoes considerable metabolism, including breakdown of the side chain and probably conjugation. The main action of this compound is irreversible inhibition of MAO (both MAOA and MAOB) this lasts for some time, and clinically is considered to have reversed within 14 days.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Microcrystalline cellulose
Pregelatinised starch
Carmellose sodium
Calcium sulfate dihydrate
Croscarmellose sodium
Magnesium stearate

Coating
Opaglos clear (which contains Shellac (E904))
Calcium carbonate (E 170)
Hypromellose
Polyethylene glycol 6000
Talc
Titanium dioxide (E171)
Ponceau 4R Lake (E124)
Carmoisine Lake (E122)
Aspartame (E951)
Sucrose

Printing Ink Composition
Shellac (E904)
Black Iron Oxide (E172)
Propylene Glycol
Ammonium Hydroxide

6.2 Incompatibilities

None

6.3 Shelf life

HDPE Container: 3 years
Alu/PVC blister pack: 3 years

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

Tablets are packed in HDPE containers with a child resistant closure and 2g silica gel canister containing 28 tablets or Alu/PVC blister strips containing 20, 28, 45, 90 or 250 tablets. Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Lime Pharma Ltd,
Mckenzie House,
Bury Street,
Ruislip,
Middlesex HA4 7TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER

PA2005/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 24th January 2014

10 DATE OF REVISION OF THE TEXT

June 2016