Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tranylcypromine 10 mg coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 10 mg tranylcypromine as tranylcypromine sulfate.

Excipient(s) with known effect
Sucrose – 66.15mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.
Off-white, round, biconvex, sugar coated tablets with an approximate diameter of 8 mm and approximate thickness of 5 mm..

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tranylcypromine is indicated for the treatment of severe depressive episodes in adult patients who have not adequately responded to at least two other antidepressant treatments.

4.2 Posology and method of administration

Treatment should take place only under supervison of a psychiatrist

Posology
Adults
Treatment should be initiated with 10 mg to 20 mg per day (10 mg in the morning **or** 10 mg in the morning and 10 mg afternoon).

Depending on efficacy and tolerability, the initial daily dose can be increased by 10 mg each week up to a therapeutic dose corresponding to the individual response and to disease severity. A dosage of 30 mg a day should only be exceeded with caution.

Resistance to treatment: If the therapeutic response is unsatisfactory, the daily dose can be further increased in steps of 10 mg every 1 to 3 weeks up to a maximum daily dose of 60 mg/day. An inpatient setting could be considered.

The total daily dose can be divided into 1 to 3 doses, and the last dose of the day should be taken no later than 3p.m, in order to avoid sleep disturbances.

When a satisfactory response has been obtained, dosage may be reduced to maintenance level often of 10 mg to 20 mg per day. In general, the average duration of treatment until response is 4 to 6 weeks. Thereafter, treatment with tranylcypromine should be continued for 4 to 6 months to avoid relapse.

When given with a tranquillizer, the dosage of tranylcypromine is not affected when given concurrently with electroconvulsive therapy; the usual dosage is 10 mg tablet twice a day during the series and 10 mg tablet a day afterwards as maintenance therapy.

Treatment with Tranylcypromine should not be discontinued suddenly as withdrawal symptoms such as anxiety, restlessness, sleep disturbances, drowsiness or delirium may occur. If applicable, treatment should be discontinued with slow reduction in dose.

Switching between antidepressants
It should be noted that for some medicinal products, a pause in treatment is necessary when switching to or from tranylcypromine.

When switching to tranylcypromine from a medicinal product that cannot be combined with tranylcypromine (see sections 4.3 and 4.5), a washout phase that is about 5 times longer than the half-life of the active substance and its active metabolites is recommended before starting treatment with tranylcypromine. The prescribing information for individual products should be consulted. The treatment with tranylcypromine should be initiated with 10 mg per day for the first week.

When switching from tranylcypromine to a medicinal product that cannot be combined with tranylcypromine (see sections 4.3 and 4.5), a 14-day pause in treatment is recommended before starting treatment with a medicinal product that is incompatible with tranylcypromine.

Elderly
In elderly patients, Tranylcypromine should be used with particular caution and initiated at the lowest dose (10 mg/day) and the dose may be increased weekly with regular monitoring of blood pressure by no more than 10 mg/day (see section 4.4).

Paediatric population:
Tranylcypromine is not indicated for children and adolescents under 18 years of age.

Patients with renal impairment
There is no sufficient data available with Tranylcypromine in the treatment of patients with impaired renal function. Therefore, patients with severe renal disorders must not be treated with Tranylcypromine (see section 4.3). Other patients with impaired renal function should be closely monitored (see section 4.4).

Patients with hepatic impairment
Tranylcypromine is contraindicated in patients with hepatic impairment (see section 4.3).

Method of administration
Oral use. Tranylcypromine should be swallowed whole with a glass of water.

4.3 Contraindications

Tranylcypromine is contraindicated in the following cases:

- hypersensitivity to the active substance or any of the excipients listed in section 6.1
- actual or suspected phaeochromocytoma
- carcinoid tumours
- actual or suspected cerebrovascular diseases
- vascular malformations (aneurysms)
- hypertension or severe cardiovascular diseases
- hepatic impairment and other liver diseases
- severe renal impairment
- porphyria
- diabetes insipidus
- patients with or a history of malignant hyperthermia
- acute delirium
- uncontrolled hyperthyroidism.

Tranylcypromine must not be administered concomitantly with, see also section 4.5.

- Selective serotonin reuptake inhibitors such as all selective serotonin reuptake inhibitors (SSRI's such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and selective serotonin-norepinephrine reuptake inhibitors (SNRI's such as venlafaxine and duloxetine)
- Tricyclic antidepressants (such as clomipramine, imipramine, amitriptyline, despiramine, nortriptyline and protriptyline)
- Tetracyclics (e.g. mirtazapine)

- Other MAO inhibitors (such as fenelzine)
- Serotonin agonists such as triptans for the treatment of migraine
- L-tryptophan
- Buspirone
- Bupropion
- Indirect sympathomimetic amines e.g. ephedrine, fenfluramine and pseudoephedrine
- Amphetamines
- Pethidine, nefopam, tramadol
- Dextromethorphan
- Levodopa.

4.4 Special warnings and precautions for use

Use tranylcypromine with regular monitoring of blood pressure in elderly patients and patients with elevated or decreased blood pressure and patients at high risk of hypertensive reactions (e.g.hyperthyroidism).

Tyramine-rich foods must not be consumed by patients on MAO inhibitor therapy which is the cause of severe hypertensive reactions (see section 4.5).

Blood sugar levels may be affected whilst on treatment with tranylcypromine, hence the insulin dosage may need to be adjusted (see section 4.5).

In epileptic patients, tranylcypromine can lower the seizure threshold and the risk for seizures may increase.

Tranylcypromine is characterised by significant acute toxicity. This must be taken into account when prescribing this medicine to patients at risk of suicide.

Tranylcypromine may aggravate some co-existing symptoms in depression such as anxiety and agitation. Use of this medicine must be stopped immediately if manic/psychotic episodes occur (see section 4.8).

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.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition may occur with tranylcypromine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St.John's Wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicinal agents that impair metabolism of serotonin (such as MAOIs e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Serotonin syndrome in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

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.

Insomnia is a frequent side effect. It may be overcome by giving the last dose of the day not later than 3 p.m. or by reducing dosage. See section 4.8.

Patients with psychiatric comorbidity
In the event of a manic mood disorder, treatment with tranylcypromine should be discontinued immediately. The same applies to the development (or worsening of existing) psychotic symptoms in patients experiencing a depressive episode with psychotic features.".

Patients with renal impairment
There is insufficient experience with tranylcypromine in patients with renal impairment. Therefore, patients with severe renal impairment must not be treated with tranylcypromine (see section 4.3). Other patients with renal impairment should be monitored closely (see section 4.2).

Elderly patients
In the treatment of elderly patients, the daily dose should be increased more slowly, with regular monitoring of blood pressure. The administered daily doses should be kept as low as possible (see section 4.2).

Excipients
Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A treatment-free interval should be observed when switching to tranylcypromine from certain medicinal products and vice versa.

When switching to tranylcypromine from a medicinal product whose concomitant use is contraindicated , a washout period of approximately 5 times the half-life of that product and its active metabolite is recommended before starting treatment with Tranylcypromine.
Conversely, after stopping tranylcypromine, a 14 day treatment break is recommended before starting treatment with a drug that is incompatible with tranylcypromine.

Medicines that affect the use of tranylcypromine
Tranylcypromine must not be used in combination with the following medicinal products (see section 4.3):

- medicinal products with marked serotonin reuptake inhibition, such as all selective serotonin reuptake inhibitors (SSRIs), clomipramine, venlafaxine, duloxetine, milnacipran, sibutramine and vortioxetine (risk of precipitation of serotonin syndrome [see section 4.4] with symptoms including hypertension, agitation and hyperthermia, sometimes with fatal outcome);
- 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;
- Tetracyclics e.g. mirtazapine;

- behavioural and neurological symptoms have been reported when MAO inhibitors and tryptophan are used concomittantly;
- serotonin agonists such as triptans used for treatment of migraine (risk of serotonin syndrome, see first bullet point);
- buspirone may increase the blood pressure sharply;
- indirectly acting sympathomimetics (contained, for example, in medicines that increase blood pressure and certain nasal, cough or cold preparations) (risk of severe hypertensive crises);
- Amphetamines (risk of severe hypertensive crisis);
- other MAOIs (risk of symptoms similar to serotonin syndrome);
- pethidine, nefopam, tramadol, dextromethorphan (dextromethorphan in antitussives agents) (possible life-threatening CNS effects or life-threatening effects on respiration or cardiovascular function);
- Levodopa (risk of an uncontrolled increase in blood pressure).

Combinations with direct-acting sympathomimetics (e.g. in cardiac stimulants to raise blood pressure, for relief from bronchospasms or in nasal drops) should be avoided.

The normally low concentrations of epinephrine or norepinephrine in local anaesthetics or eye drops do not pose a particular risk in patients treated with tranylcypromine, since an alternative degradation pathway via catechol-O-methyltransferase is possible. Combination with selective ß2-sympathomimetics for inhalation use is likewise associated with no particular risk.

Potential of tranylcypromine to affect other medicinal products
The antihypertensive effects of medicines used to treat high blood pressure (e.g. guanethidine, methyldopa) can be aggrevated by tranylcypromine; in some cases, an increase in blood pressure (with states of agitation) can occur.

The effect of insulin and oral antidiabetics may be potentiated (see section 4.4).

Adverse reactions of bupropion (or amfebutamone – a smoking cessation agent), such as seizures and agitation, may be exacerbated by the concomitant ingestion of tranylcypromine. This combination must not be used (see section 4.3).

The effects of CNS-depressant medicines (neuroleptics, antidepressants, analgesics, benzodiazepines) may be potentiated by concomitant administration of tranylcypromine.

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 antihistamines, since antimuscarinic and sedative effects of antihistamines are increased by MAOIs.

Caution is advised with concomitant buprenorphine due to the risk of serotonin syndrome (see section 4.4).

During surgery:
Patients treated with tranylcypromine must not undergo operations requiring general anaesthesia.
Also, they should not be given cocaine or local anaesthesia containing vasoconstrictors.Tranylcypromine may potentiate the hypotensive effects of spinal anaesthesia.

Use of tranylcypromine must be stopped two weeks before surgery due to potentially dangerous interactions with certain anaesthetics.

Dietary precautions

Tranylcypromine leads to the inhibition of an enzyme system (MAO inhibition) required for the detoxification of biogenic amines. High levels of tyramine in certain foods have caused severe hypertensive reactions in patients treated with MAO inhibitor therapy (See 4.8).
Regardless of the MAOI dose, foods containing high amounts of tyramine (e.g. air-cured, fermented or aged meat, sausages, salami, fish or poultry, mature cheese, broad beans, fish sauces, all fermented soy products, yeast extracts, fermented beverages like beer or wine) should be avoided 1 day before, during and for 14 days after treatment with tranylcypromine.

The effect of alcohol may be increased with concomitant ingestion of Tranylcypromine.

Dietary advice should be discussed with the patient by a specialized dietician who has knowledge of psychiatric diseases and psychopharmaceuticals.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
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.

Fertility
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

The following undesirable effects may occur with the use of Tranylcypromine in the following frequencies:
Rare (≥1/10,000 to <1/1,000);
Not known (cannot be estimated from the available data).
The following effects have been reported and are listed below by body system:

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Blood disorder
Psychiatric disorders	Rare Not known	Hallucination Hypomania Drug dependence[1] Insomnia[2] Anxiety Agitation, Suicidal ideation[6] Suicidal behaviour[6] Restlessness
Nervous system disorders	Rare Not known	Neuropathy peripheral Dizziness Somnolence Headache Sleep disorder Throbbing headache[5]
Eye disorders	Not known	Vision blurred
Cardiac disorders	Not known	Palpitations
Vascular disorders	Not known	Orthostatic hypertension[3] Hypertensive crisis[4]
Gastrointestinal disorders	Not known	Dry mouth Diarrhoea Nausea Vomiting
Hepatobiliary disorders	Rare	Hepatocellular injury Jaundice

Skin and subcutaneous tissue disorders	Not known	Rash
General disorders and administration site conditions	Rare	Drug tolerance[1] Fatigue
	Not known	weight gain Fluid retention

[1]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.
[2] see section 4.4
[3]Postural hypertension (which is usually temporary, but if it persists the drug should be stopped)
[4]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.
[5]Throbbing headache may be an early warning of hypertensive crisis.
[6]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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms:
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.

Management:
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. In hypertensive crisis (e.g. acute increase in blood pressure to more than 180/100 mm Hg), the use of conventional oral or parenteral antihypertensive agents is indicated.
Tyramine-induced hypertensive crisis are treated in the same manner as other hypertensive crisis, and in an adjusted setting of continuous medical surveillance.
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

Pharmacotherapeutic group: Non-selective Monoamine Oxidase Inhibitor.
ATC code: N06AF04
Tranylcypromine is a non-Hydrazine monoamine oxidase inhibitor.

5.2 Pharmacokinetic properties

Absorption
Tranylcypromine is rapidly absorbed after oral administration.

Distribution
Peak plasma levels are reached after about 2.5 hours and the half life is of the order of 2 hours.

Biotransformation

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.

Elimination
Excretion is pH dependent.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Calcium sulfate dihydrate
Sucrose
Maize starch
Carmellose
Magnesium stearate

Coating
Gelatin
Purified water
Sucrose
Talc
Maize starch
Calcium carbonate
Titanium dioxide (E171)
Carnauba wax

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

4 years

In use shelf life: discard 28 days after opening

6.4 Special precautions for storage

Store below 30^{o}C. Store in the original package.

6.5 Nature and contents of container

Blister pack consisting of PVC sheet and Al foil or PVC/PVDC sheet and Al foil.
HDPE bottle with HDPE moisture-proof child resistant closure.

Pack size: 1, 8, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 100 or 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
11 Boumpoulinas Street
Nicosia
1060
Cyprus

8 MARKETING AUTHORISATION NUMBER

PA1567/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: