Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Parnate 10 mg coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 10mg tranylcypromine as tranylcypromine sulfate.

Excipients with known effect:
6.12mg of sucrose per tablet

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.
Light red coloured, bi-convex, film coated tablets.

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

Posology:
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:
Use with great caution and at a lower dosage
Paediatric population:
Tranylcypromine is not indicated for children under 18 years of age.

Method of administration**:**
Parnate 10mg Tablets are for oral administration only.
The coated tablets should be taken with some liquid (preferably with half a glass to a full glass of water).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 damage or blood dyscrasias.

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.
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.

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

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

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

Parnate 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 Not known	Drug tolerance[1] Fatigue 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 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. 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

Pharmacotherapeutic group: 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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cores
Sucrose
Maize Starch
Calcium sulfate dihydrate
Erythrosine (E127)
Magnesium Stearate

Gelatin

Coating
Opadry Red 06H250000 (PI 106298)
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25˚C. Store in the blister packs. Keep the blister packs in the outer carton in order to protect from light and moisture

6.5 Nature and contents of container

PVC-PVDC / Aluminium blisters in a Carton containing 28 (7 tablets/blister x 4) or 50 **(**10 tablets/blister x 5) tablets. Not all pack sizes may be marketed.

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.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited, Unit 17, Northwood House, Northwood Crescent, Northwood, Dublin 9, D09 V504, Ireland.

8 MARKETING AUTHORISATION NUMBER

PA1142/035/001

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