

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 sulphate.

Excipients: contains 3.2mg of Carmoisine (E122) and Ponceau 4R (E124) and 55.04mg of sucrose per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

Geranium-red coloured, biconvex, sugar -coated tablets marked 'FW251' on one side only.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Parnate is indicated for use in the management of depression but excluding mild depressive states resulting from temporary situational difficulties.

4.2 Posology and method of administration

Route of administration: Oral

Adults only: The usual daily dosage is 20mg in divided doses (morning and afternoon) with a subsequent increase to 30mg if necessary (additional tablet at mid-day). After optimal control, the maintenance dose is reached by gradual decrements, usually to a level of 10mg daily. When used during electroconvulsive therapy the usual dose is 10mg twice daily during the course and 10mg daily thereafter.

Elderly (over 65 years): Use with great caution and often at lower dosage than for adults.

Children:

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

4.3 Contraindications

Tranylcypromine should not be given to anyone who is hypersensitive to any of the ingredients or with phaeochromocytoma, cerebrovascular disease, congestive heart failure, a history of liver disease or with abnormal liver function tests.

Tranylcypromine is not indicated in the manic phase.

It should not be administered at the same time as, or within 14 days of, treatment with other MAOIs, buspirone, or dibenzazepine derivative drugs (including tricyclic antidepressant agents, perphenazine or carbamazepine). In the cases of clomipramine and imipramine, 3 weeks should be left before starting tranylcypromine therapy. It is recognized that there is some division of consultant opinion with respect to concomitant use of MAOIs and tricyclic antidepressants as well as other antidepressant combinations in resistant patients.

Tranylcypromine should not be taken by patients suffering from porphyria.

There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when serotonin reuptake inhibitors or serotonin/noradrenalin inhibitors (eg venlafaxine) have been combined with MAOIs. In general it is recommended that sufficient time is allowed for clearance of active drug and metabolites before a second trial of antidepressant is commenced. For example, five weeks in the case of fluoxetine and two weeks with paroxetine. Conversely, these drugs should not be started within 14 days of discontinuing tranylcypromine. Extreme caution is advised for any combination of drugs trialed for potentiating therapeutic effects in depression.

Tranylcypromine should not be used in combination with guanethidine, dextromethorphan, or with CNS depressants such as alcohol and narcotic analgesics. Death has been reported in patients receiving a single dose of pethidine.

4.4 Special warnings and precautions for use

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.

Use Parnate with great caution in patients who are elderly or who have cardiovascular disease, epilepsy (as tranylcypromine has a variable effect on the convulsive threshold), liver dysfunction, or those with a previous history of dependence on drugs and alcohol.

Patients should be specifically asked if they are taking any other medication because of the possibility of drug interactions.

Parnate should be discontinued at least two weeks before elective surgery /dentistry because of the potential for interaction. It should not be given with cocaine or local anaesthesia containing sympathomimetic vasoconstrictors. Hypotension may result after spinal anaesthesia.

Tranylcypromine should be used with caution in agitated patients or those who have cardiovascular disease, epilepsy, blood dyscrasias or diabetes; and in patients taking diuretics.

Blood pressure should be monitored to detect any pressor response and therapy discontinued if palpitations or headaches occur. Postural hypotension may occur. Hypotensive side effects may occur even in hypertensive as well as normotensive patients. Due to the possibility of patients undergoing "Withdrawal Syndrome" (see section 4.8 Undesirable effects) abrupt withdrawal of tranylcypromine should be avoided.

Tranylcypromine may cause excessive stimulation in schizophrenic patients and may provoke mania in manic-depressive patients. Caution is advised in patients undergoing electroconvulsive therapy (ECT).

This product contains the following excipients which may cause reactions.

Sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-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

Patients should be warned about self medication (including cold and cough cures, hay fever medications, anti-appetite medicines, weight-reducing preparations and “pep” pills) and about potential food interactions.

Patients under treatment with tranlycypromine should avoid high protein food that has undergone breakdown by ageing, fermentation, pickling, smoking or bacterial contamination. Patients should avoid cooked or plain cheese, Oxo, Bovril, Marmite, brewer’s yeast, etc during treatment and up to 14 days after ceasing treatment. Flavoured textured vegetable protein, hung game, pickled herrings, dry sausage (salami, pepperoni etc), liver, yoghurt, broad bean pods, fermented soya bean extract and excessive amounts of chocolate may also present a hazard. Patients should not consume alcoholic drink or non- alcoholic beers, lagers and wines and excessive amounts of tea and coffee should be avoided.

Where a reaction between tranlycypromine and certain foodstuffs occurs the intensity of the reaction is usually related to the tyramine content of the food. The reaction is now well recognized and serious hypertensive episodes are extremely rare. Should such a reaction occur, the hypertension should be controlled by slow administration of phentolamine 5mg to 10mg IV, repeated if necessary. Care should be taken to administer this drug slowly to avoid an excessive hypotensive effect.

Tranlycypromine may potentiate the effects of alcohol.

Tranlycypromine may potentiate the action of pethidine, morphine, adrenaline, amphetamines and other sympathomimetic amines such as fenfluramine, ephedrine, phenylpropanolamine, dopamine and levodopa (see also Contraindications). Tranlycypromine may also potentiate the effects of antihypertensives, hypoglycaemic agents, sympathomimetics, anti-Parkinson drugs, antimuscarinics, local anaesthetics and CNS depressants, including barbiturates.

It is suggested that MAOIs are not administered at the same time as, or within 14 days of, treatment with amfebutamone (bupropion) or 5HT₁ agonists.

It is suggested that MAOIs are not administered at the same time as anti-epileptics, altretamine, doxapram, tetrabenazine, oxypertine or clozapine.

The combination of MAOIs and tryptophan has been reported to cause behavioural and neurological symptoms.

4.6 Fertility, pregnancy and lactation

This drug should not be used in pregnancy unless considered essential by the physician. There is no evidence in relation to safety of use in human beings. The drug passes into the milk in lactating dogs.

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

Throbbing headache may be an early warning of hypertensive crisis.

Side-effects tend to be mild or moderate in severity, often subsiding as treatment continues, and can often be minimized by adjusting dosage.

The most important reaction potentially is hypertensive crisis as this has been potentially fatal or resulted in intracranial bleeding.

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

Common side- effects include: dizziness, drowsiness, weakness and fatigue, oedema, gastrointestinal disturbances (nausea, vomiting, dry mouth, constipation), insomnia, blurred vision, altered driving ability, postural hypotension, twitching, myoclonic movements, hyperreflexia, elevated serum transaminases and anorgasmia.

Uncommon side-effects are headache, nervousness, euphoria, paraesthesia, sweating, increased appetite and weight, rash, pruritis, difficulty in micturition, muscle tremor, peripheral neuritis, behavioural changes, arrhythmias, convulsions, impotence and delayed ejaculation, purpura, blood dyscrasias, jitteriness, palilalia, nystagmus, hypernatraemia, glaucoma, lupus-like illness, confusion, hallucinations and elevated liver enzymes.

Other severe effects are rare and include: ataxia, shock-like coma, toxic delirium, neuroleptic malignant syndrome (occasionally fatal), manic reaction, acute anxiety reaction, precipitation of schizophrenia, transient respiratory and cardiovascular depression following ECT, fatal progressive necrotizing hepatocellular damage, reversible jaundice, hypermetabolic syndrome, oedema of the glottis and fever associated with increased muscle tone.

Hyponatraemia (usually in the elderly and maybe due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

Withdrawal may be associated with nausea, vomiting and malaise. An uncommon withdrawal syndrome following abrupt withdrawal of tranylcypromine has been reported. Signs and symptoms start 24 to 72 hours after drug discontinuation and may vary from vivid nightmares and agitation to frank psychosis and convulsions. This will respond usually to restitution of low dose tranylcypromine, followed by cautious downward titration and discontinuation.

4.9 Overdose

Signs and symptoms may be absent or minimal during the initial 12 hour period after ingestion and may be slow to develop, reaching a maximum in 24 to 48 hours. Death has been reported after overdose, so immediate hospitalisation with continuous observation is essential. Large doses may cause hypomania, euphoria, followed by coma with hypotension or acute hypertension with subarachnoid haemorrhage. Sometimes extrapyramidal symptoms occur.

Other symptoms are: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, rigidity, convulsions, rapid and irregular pulse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis and cool, clammy skin.

Treatment involves gastric lavage with charcoal slurry in early poisoning (tablet dissolve slowly in stomach). Bed rest, raised feet with hypotension, avoidance of vasopressors and hypnotics (including morphine, pethidine and barbiturates) is advised. Phentolamine IV is given for hypertension. Body temperature should be monitored and fever should be cooled. Fluid and electrolyte balance must be maintained and IV diazepam is used for CNS stimulation. IV hydrocortisone may be used for coma or severe hypotension.

There is no specific treatment for overdose. Haemodialysis, peritoneal dialysis and charcoal haemoperfusion may help but data is insufficient to corroborate their use.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tranylcypromine is a non-hydrazine monoamine oxidase inhibitor.

5.2 Pharmacokinetic properties

Tranylcypromine is well and rapidly absorbed. The drug is extensively metabolised in the liver and eliminated mainly in urine with a $T_{1/2}$ of about 2 hours. Recovery from the inhibition of the monoamine oxidase is usually achieved by 14 days.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cores

Sucrose
Maize starch
Calcium sulphate dihydrate
Carmellose sodium
Magnesium stearate

Coating

Gelatin
Sucrose
Docusate Sodium
Purified talc
Light kaolin
Calcium carbonate
Ethylcellulose
Acacia
Carmoisine (E122)
Ponceau 4R (E124)
Maize starch
Titanium dioxide (E171)
Carnauba wax
Edible ink (shellac, iron oxide black (E172), soya lecithin (E322) and trace amounts of dimethyl siloxane)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container in the outer carton to protect from light and tightly closed to protect from moisture.

6.5 Nature and contents of container

Polypropylene tablet container with cap and security tag containing desiccant cartridge and 28 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.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 899/16/1

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Date of last renewal: 1st April 2008

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