NAME OF THE MEDICINE

Tranylcypromine sulfate

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CAS no: 13492-01-8

DESCRIPTION

Parnate tablets are ‘geranium rose’ coloured, biconvex film-coated tablets.

Each tablet contains tranylcypromine 10 mg as the sulphate. Parnate tablets also contain the following excipients: calcium sulfate, starch - maize, sucrose, erythrosine CI45430, magnesium stearate, gelatin, Opadry complete film coating system 06H250000 Red, carnauba wax.

Tranylcypromine sulphate is a white or almost white, crystalline powder, soluble in water; very slightly soluble in ethanol (96%) and in ether.

Name: (1RS,2SR)-2-phenyl-cyclopropylamine sulphate

Molecular formula: \((C_9H_{11}N)_2H_2SO_4\)

Molecular weight: 364.5

PHARMACOLOGY

Tranylcypromine is a non-hydrazine monoamine oxidase inhibitor with a rapid onset of activity. It increases the concentration of adrenaline, noradrenaline, and serotonin in storage sites throughout the nervous system, and in theory, this increased concentration of monoamines in the brainstem is the basis for its antidepressant activity. When tranylcypromine is withdrawn, monoamine oxidase activity is recovered in 3 to 5 days, although the drug is excreted in 24 hours.

INDICATIONS

Parnate is indicated for the treatment of Major Depression.
CONTRAINDICATIONS

BECAUSE THE EFFECT OF MANY ANTIDEPRESSANT DRUGS MAY PERSIST FOR SEVERAL DAYS, DO NOT COMMENCE PARNATE THERAPY WITHIN LESS THAN A WEEK OF DISCONTINUING TREATMENT WITH SUCH DRUGS. THEN USE HALF THE NORMAL DOSAGE FOR THE FIRST WEEK. SIMILARLY, ALLOW AT LEAST A WEEK TO ELAPSE BETWEEN THE DISCONTINUANCE OF PARNATE AND THE ADMINISTRATION OF ANY OTHER DRUG THAT IS CONTRAINDICATED WITH PARNATE.

PARNATE IS CONTRAINDICATED:

- In patients with a known hypersensitivity to tranylcypromine or any of its components.

- In combination with other MAO inhibitors, such as phenelzine and moclobemide (marketed in Australia), furazolidone, iproniazid, isocarboxazid, nialamide, pargyline, and procarbazine hydrochloride.

- In combination with dibenzazepine (tricyclic) antidepressants, such as amitriptyline, clomipramine, desipramine, dothiepin, imipramine, nortriptyline, trimipramine and doxepin, or in combination with carbamazepine and doxepin as these combinations may induce hypertensive crises or severe convulsive seizures. Tetracyclic antidepressants should also be avoided.

- In combination with sympathomimetics including amphetamines, fenfluramine, ephedrine, phenylpropanolamine and over-the-counter drugs such as cold, hayfever and weight-reducing preparations that contain vasoconstrictors, as severe hypertensive reactions may result. Also, methyldopa, dopamine, levodopa and tryptophan as they may result in potentiation, precipitating hypertension, severe headache and hyperpyrexia; cerebral haemorrhage may occur.

- With pethidine and closely related narcotic analgesics, as respiratory depression, hypotension, restlessness and coma may ensue.

- In combination with dextromethorphan. The combination of MAOIs and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behaviour.

- In combination with fluoxetine and other Selective Serotonin Reuptake Inhibitors (SSRIs). There have been reports of serious, sometimes fatal, reactions in patients receiving fluoxetine in combination with MAOIs and in patients who have recently discontinued fluoxetine prior to the commencement of MAOI therapy. Therefore, Parnate should not be used in combination with fluoxetine, or its congeners. Allow at least five weeks between discontinuation of fluoxetine and initiation with Parnate, as fluoxetine and its major metabolite have very long half lives. Fluoxetine should not be given within two weeks of Parnate discontinuation. Parnate should not be given together with or within two weeks of treatment with other SSRIs (paroxetine, sertraline).

- In combination with buspirone hydrochloride. Parnate should not be used in combination with buspirone hydrochloride since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone hydrochloride. At least 10 days should elapse between the discontinuation of Parnate and the institution of buspirone HCl.
- **In combination with cheese or other foods with a high tyramine content.** Hypertensive crises have sometimes occurred during Parnate therapy after ingestion of foods with a high tyramine content. It is therefore important that patients be told to avoid matured cheese and protein extracts such as Marmite, Vegemite, Bonox, Bovril etc. Other foods to be avoided are the pods of broad beans which contain levodopa, sauerkraut, pickled herring, sour cream, soy sauce, avocado pears, yeast extracts and banana skins. Alcoholic drinks, which may contain significant amounts of tyramine, especially red wine such as Chianti, should also be avoided.

In general, the patient should avoid protein foods in which ageing or protein breakdown is used to increase flavour. Patients must also be warned against self-medication with proprietary drugs such as cold, hay fever or weight-reducing drugs that contain pressor agents.

- **In patients with cerebrovascular or cardiovascular disease, a history of recurrent or frequent headaches, liver damage or blood dyscrasias.** Parnate should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease or hypertension. Parnate should not be used in patients with known liver damage or blood dyscrasia.

- **In patients with phaeochromocytoma.** Parnate should not be used in the presence of phaeochromocytoma, or if it is suspected, as such tumours secrete pressor substances.

- **In the elderly.** Parnate should not be administered to any patient beyond 60 years of age because of the possibility of existing cerebral sclerosis with damaged blood vessels.

- **In patients with impaired hepatic function.** Parnate should not be used in patients with a history of liver disease or in those with abnormal liver function tests.

**PRECAUTIONS**

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs.

The risk is increased in young adults aged 18 - 24 years, as improvement may not occur during the initial treatment period (usually one to two months). Patients should be closely monitored for clinical worsening of suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening of suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistent or whose emergent suicidality is severe, abrupt in onset or was not part of the patient’s presenting symptoms.
Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves, and to seek medical advice immediately if these symptoms present. Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 - 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorders (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorders and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescents patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorders as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

**Mania and bipolar disorder**

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that tranylcypromine is not approved for use in treating bipolar depression.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorders or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.
Prescriptions for Parnate should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

LIKE ALL POWERFUL DRUGS, PARNATE MAY OCCASIONALLY PROVOKE SERIOUS SIDE EFFECTS. IF PATIENTS ARE KEPT UNDER REGULAR AND FREQUENT OBSERVATION, THE DRUG CAN BE STOPPED PROMPTLY SHOULD ANY ADVERSE REACTIONS OCCUR. IT IS IMPORTANT FOR THE PHYSICIAN TO BE FULLY AWARE OF THE SIDE EFFECTS, CONTRAINDICATIONS AND CAUTIONS DESCRIBED IN THE PRESCRIBING INFORMATION.

Caution is required when giving Parnate in the following conditions
- **Diabetes.** Some MAO inhibitors have contributed to hypoglycaemic episodes in diabetic patients receiving insulin or oral hypoglycaemic agents. Parnate should therefore be used with caution in diabetics under treatment with these drugs.
- **Epileptic patients.** Because the influence of tranylcypromine on the convulsive threshold is variable in animal experiments, suitable precautions should be taken if epileptic patients are treated with Parnate.
- **Surgery.** Although excretion of tranylcypromine is rapid, it is advisable wherever possible to discontinue Parnate therapy at least 10 days before surgery, because of possible interference with the action of certain anaesthetics and analgesics.
- **Hyperthyroid patients.** These patients have increased sensitivity to pressor amines.
- **Patients with angina.** MAO inhibitors have the capacity to suppress anginal pain that would otherwise serve as a warning of myocardial ischaemia.
- **Impaired renal function.** There is a possibility of cumulative effects in patients with impaired renal function.

**Effects on fertility**
No information available.

**Use in pregnancy**
(Category B2)
Adequate human data on use during pregnancy and adequate animal reproduction data are not available. Use of any drug in pregnancy requires that the potential benefits of the drug be weighed against its possible hazards to mother and child. Animal reproductive studies show that tranylcypromine passes through the placental barrier into the fetus of the rat.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of antidepressants in pregnancy.

Neonates exposed to antidepressants late in the third trimester have shown drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of antidepressants in pregnancy may be associated with an increase in pre-term delivery.
Use in lactation
Adequate human data on use during lactation and adequate animal reproduction data are not available. Tranylcypromine is secreted into breast milk of lactating mothers but the clinical significance of this has not been fully evaluated.

Therefore, tranylcypromine should be used in lactating women only if clearly needed and if the potential benefits justify the potential risk.

Paediatric use
The safety and efficacy of Parnate for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Parnate should not be used in this age group for the treatment of depression or other psychiatric disorders.

Use in the elderly
Refer to Contraindications.

Carcinogenicity
No information available.

Genotoxicity
No information available.

Interactions with other medicines
Exercise caution when giving Parnate with the following drugs:

- **Guanethidine**, as its action may be antagonised;
- **Reserpine**, as hyperactivity may occur;
- **Other hypotensive agents**, because of the possibility of additive hypotensive effects;
- **Barbiturates**, as their action may be prolonged or potentiated;
- **Anti-Parkinsonism agents**, as the combination may result in potentiation, with profuse sweating, tremulousness, and rise in body temperature;
- **Clomipramine hydrochloride**, as this drug, in combination with a MAO inhibitor, has been reported to result in hyperpyrexia, diffuse intravascular coagulation, and status epilepticus;
- **Anticoagulants**, as some animal studies have suggested that the effect of anticoagulants may be potentiated if a MAO inhibitor is given concurrently. One suspected case of potentiation has been reported in man.

Patients should be advised not to consume excessive amounts of caffeine in any form.

Refer to Contraindications for further information.

Effect on laboratory tests
No information available.

Driving or operating machinery
Parnate may affect the ability to drive or operate machinery.
ADVERSE EFFECTS

The most important adverse effect associated with Parnate is the occurrence of hypertensive crises which have sometimes been fatal.

Cases of sudden paroxysmal rise in blood pressure have occurred, notably in association with foods containing tyramine. These crises are characterised by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea or vomiting, sweating with early pallor followed later by flushing. Either tachycardia or bradycardia may be present; and associated mydriasis may also occur. This headache, together with pain and stiffness in the cervical muscles, may mimic subarachnoid haemorrhage, but can equally be associated with actual intracranial bleeding, as in other conditions where a sudden rise in blood pressure occurs. Cases of such bleeding have been reported, some of which have been fatal.

Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headache during Parnate therapy. These signs may be prodromal of a hypertensive reaction. Patients should be instructed to report promptly the occurrence of headache or other symptoms.

Recommended treatment in hypertensive reactions

If a hypertensive reaction occurs, Parnate should be discontinued and therapy to lower blood pressure should be instituted immediately, if indicated. Headache tends to abate as blood pressure falls. On the basis of present evidence, phentolamine is recommended (the dosage reported for phentolamine is 5 mg i.v.). Reserpine should not be used. Care should be taken to administer this drug slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling. Other symptomatic and supportive measures may be desirable in particular cases. Acute symptoms generally subside within 24 hours.

Other side effects

The most frequently seen side effect is insomnia, which can usually be overcome by giving the last dose of the day not later than 3 pm, by reducing the dose, or by prescribing a mild hypnotic. Occasional cases of dizziness, palpitation, weakness, dry mouth and drowsiness have been reported, as have nausea, diarrhoea, abdominal pain and constipation. Most of these effects can be relieved by lowering the dosage or by giving suitable concomitant medication.

Palpitations or unusually frequent headaches, unaccompanied by paroxysmal hypertension, may possibly be dose-related in some patients. Such symptoms may respond to reduction of dosage. If improvement is not rapid, the drug should be discontinued.

Hypotension, which may be postural, has been observed during Parnate therapy. Syncope has been rarely seen. Dosage should not be increased in the presence of hypotension. This side effect is usually temporary, but if it persists, the drug should be discontinued. The blood pressure will then return rapidly to pre-treatment level.

Tachycardia, significant anorexia, oedema, blurred vision, chills and impotence have each been reported.

Impaired water excretion compatible with the syndrome of inappropriate secretion of antidiuretic hormone (IADH) has been reported.
Overstimulation, which may include increased anxiety and agitation, and manic symptoms, may sometimes occur with normal dosage but is more commonly associated with overdosage. Reduction of the dose is indicated. In certain instances it may be helpful to administer a sedative phenothiazine tranquilliser, such as chlorpromazine, concomitantly.

There is a risk of dependency development. Withdrawal symptoms may be anticipated.

Rare instances of hepatitis and skin rash have been reported.

Tinnitus, muscle spasm, tremors, myoclonic jerks, numbness, paraesthesia, urinary retention and retarded ejaculation have been reported.

Haematological disorders including anaemia, leukopenia, agranulocytosis and thrombocytopenia have been reported.

**DOSAGE AND ADMINISTRATION**

(Adults Only)

Begin with 20 mg a day - given as 10 mg in the morning and in the afternoon.

If there is no satisfactory response after two weeks, add one more tablet at midday. Continue this dosage for at least a week. A dosage of 3 tablets a day should only be exceeded with caution, and the maximum dose should not exceed 30 mg/day. When a satisfactory response is established, dosage may be reduced to a maintenance level. Some patients will be maintained on 20 mg per day, some will need only 10 mg daily. If no improvement occurs, continued administration is unlikely to be beneficial.

When given together with a tranquilliser, the dosage of Parnate is not affected. When the drug is given concurrently with electroconvulsive therapy, the recommended dosage is 10 mg twice a day during the series and 10 mg a day afterwards as maintenance therapy.

**OVERDOSAGE**

**Symptoms**

The characteristic symptoms that may be caused by overdosage are usually those described under Adverse Effects. Tachycardia, sweating and hyperpyrexia with restlessness and excitement are usually produced. Depression, stupor or coma may, however, be present or develop. Blood pressure may be raised, but hypotension may supervene.

**Treatment**

Gastric lavage is helpful if performed early. Treatment should normally consist of general supportive measures, close observation of vital signs and steps to counteract specific symptoms as they occur since MAO inhibition may persist. The management of hypertensive reactions is described under Adverse Effects.
External cooling is recommended if hyperpyrexia occurs. Barbiturates have been reported to help myoclonic reactions, but frequency of administration should be controlled carefully because Parnate may prolong barbiturate activity. When hypotension requires treatment, the standard measures for managing circulatory shock should be initiated. If pressor agents are required, noradrenaline is the most suitable; however, its action may be potentiated, and the rate of infusion should be regulated by careful observation of the patient. Metaraminol may be required if marked refractory hypotension occurs (left ventricular failure should be excluded).

A successful recovery following haemodialysis after a self-administered overdosage of 350 mg of tranylcypromine has been reported.

PRESENTATION AND STORAGE CONDITIONS

Parnate tablets
- Film-coated tablets containing tranylcypromine 10 mg (as the sulphate)
- Blister packs of 50 tablets

Store below 25°C.

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NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 6 October 2010
Date of most recent amendment: 09 July 2012

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