

NEW ZEALAND DATA SHEET

1. NARDIL® 15 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated phenelzine sulfate tablet contains phenelzine sulfate equivalent to 15 mg phenelzine base.

Phenelzine sulfate

Molecular weight: 234.27

Chemical formula: C₈H₁₂N₂·H₂SO₄

CAS Number: 156-51-1

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Orange, film coated biconvex tablets with round edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of major depression.

Phenelzine sulfate should rarely be the first antidepressant medicine used. Rather it is more suitable for use with patients who have failed to respond to the medicines more commonly used for these conditions.

4.2 Dose and method of administration

Dose

Initial dose

The usual starting dose of phenelzine sulfate is one tablet (15 mg) three times a day.

Early phase treatment

Dosage should be increased to at least 60 mg per day at a fairly rapid pace consistent with patient tolerance. It may be necessary to increase dosage up to 90 mg per day to obtain sufficient MAO inhibition. Many patients do not show a clinical response until treatment at 60 mg has been continued for at least 4 weeks.

Maintenance dose

After maximum benefit from phenelzine sulfate is achieved, dosage should be reduced slowly over several weeks. Maintenance dose may be as low as one (1) tablet, 15 mg, a day or every other day, and should be continued for as long as required.

Special populations

Elderly

As for adults.

Postural hypotension may be an unwanted effect of MAOIs in the elderly. Elderly patients as a group tend to receive multiple drug therapies and the possibility of increased risk of drug interactions should be borne in mind. Nardil should only be used with great caution in elderly patients.

Paediatric population

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The safety and efficacy of Nardil for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Nardil should not be used in this age group for the treatment of depression or other psychiatric disorders. (Please refer to section 4.4).

Method of administration

Oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Phenelzine sulfate should not be used in patients with phaeochromocytoma, cerebrovascular disease, congestive heart failure, a history of liver disease, or with abnormal liver function tests.

MAO inhibitors including phenelzine sulfate are contraindicated in patients receiving guanethidine.

Patients taking phenelzine sulfate should not undergo elective surgery requiring general anaesthesia. Also, they should not be given cocaine or local anaesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of phenelzine sulfate and spinal anaesthesia should be kept in mind. Phenelzine sulfate should be discontinued at least 10 days prior to elective surgery.

Phenelzine sulfate should not be used in combination with selective serotonin reuptake inhibitors (SSRIs) serotonin-noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs) [see section 4.5].

Phenelzine is not indicated in the manic phase.

4.4 Special warnings and precautions for use

Clinical Worsening and Suicide Risk

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. 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 co-morbid 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 4400 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

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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, there was a reduction with antidepressants compared to the 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 health care 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.

Prescription for Nardil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

General

In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. It is recommended that careful observations of patients undergoing phenelzine sulfate treatment be maintained until control of depression is achieved. If necessary, additional measures (ECT, hospitalisation, etc.) should be instituted.

Caution should be exercised if the patient undergoes concurrent electroconvulsive therapy (ECT).

All patients undergoing treatment with phenelzine sulfate should be closely followed for symptoms of postural hypotension. Hypotensive side effects have occurred in hypertensive as well as normotensive and hypotensive patients. Blood pressure usually returns to pre-treatment levels rapidly when the medicine is discontinued or the dosage is reduced.

Because the effect of phenelzine sulfate on the convulsive threshold may be variable, adequate precautions should be taken when treating epileptic patients.

Phenelzine sulfate may cause excessive stimulation in schizophrenic patients; in manic-depressive states it may result in a swing from a depressive to a manic phase.

Phenelzine sulfate should be used with caution in combination with anti-hypertensive medicines, including thiazide diuretics and beta-blockers, since exaggerated hypotensive effects may result.

There is conflicting evidence as to whether or not MAO inhibitors affect glucose metabolism or

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potentiate hypoglycaemic agents. This should be kept in mind if phenelzine sulfate is administered to diabetics.

Warning to the Patient

All patients should be warned that the following foods, beverages, and medications must be avoided while taking phenelzine sulfate, and for two weeks after discontinuing use.

Foods and Beverages to Avoid:

Meat and fish: Pickled herring, liver, dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna).

Vegetables: Broad bean pods (fava bean pods) and sauerkraut

Dairy Products: Cheese, yoghurt (cottage cheese and cream cheese are allowed)

Beverages: Beer, wine, alcohol-free and reduced alcohol beer and wine products

Miscellaneous: Yeast extract (including brewer's yeast in large quantities), meat extract, excessive amounts of caffeine and chocolate, any spoiled or improperly refrigerated, handled or stored protein-rich foods such as meats, fish, and dairy products, including foods that may have undergone protein changes by aging, pickling, fermentation, or smoking to improve flavour.

Medications to Avoid:

- Cold and cough preparations (including those containing dextromethorphan)
- Nasal decongestants (tablets, drops or spray)
- Hay-fever medications
- Sinus medications
- Asthma inhalant medications
- Anti-appetite medicines
- Weight-reducing preparations
- "Pep" pills
- Tryptophan-containing preparations
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-noradrenaline reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)

Certain prescription medicines should be avoided. Therefore, patients under the care of another physician or dentist, should inform him/her that they are taking phenelzine sulfate.

Patients should be warned that the use of the above foods, beverages, or medications may cause a reaction characterised by headache and other serious symptoms due to a rise in blood pressure, with the exception of dextromethorphan which may cause reactions similar to those seen with pethidine.

Patients should be instructed to report promptly the occurrence of headache or other unusual symptoms.

Development of serotonin syndrome may occur in association with treatment with MAOIs particularly when given in combination with SSRIs and SNRIs, or other serotonergic agents.

Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with phenelzine sulfate should be discontinued if such events occur and supportive symptomatic treatment initiated.

4.5 Interaction with other medicines and other forms of interaction

The potentiation of sympathomimetic substances and related compounds by MAO inhibitors may result in hypertensive crises (see Adverse Effects). Therefore, patients being treated with phenelzine sulfate should not take sympathomimetic medicines (including amphetamines, cocaine, methylphenidate hydrochloride, dopamine, adrenaline, noradrenaline and ephedrine) or related

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compounds (including methyldopa, levodopa, tryptophan, L-tyrosine and phenylalanine).

Hypertensive crises during phenelzine sulfate therapy may also be caused by the ingestion of foods with a high concentration of tyramine or dopamine. Therefore, patients being treated with phenelzine sulfate should avoid high protein food that has undergone protein breakdown by aging, fermentation, pickling, smoking, or bacterial contamination. Patients should avoid cheeses (especially aged varieties), pickled herring, beer, wine, liver, yeast extract (including brewer's yeast in large quantities), dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna), pods of broad beans (Fava beans) and yoghurt. Excessive amounts of caffeine, and chocolate may also cause hypertensive reactions.

Phenelzine sulfate should not be used in combination with dextromethorphan or with CNS depressants such as alcohol and certain narcotics (including pethidine and propoxyphene). Excitation seizures, delirium, hyperpyrexia, circulatory collapse, coma, and death have been reported in patients receiving MAO inhibitor therapy who have been given a single dose of pethidine. Phenelzine sulfate should not be administered together with or in rapid succession to other MAO inhibitors, or dibenzazepine derivative medicines because hypertensive crises and convulsive seizures, fever, marked sweating, excitation, delirium, tremor, coma, and circulatory collapse may occur.

Dibenzazepine derivative medicines include nortriptyline hydrochloride amitriptyline hydrochloride, perphenazine, clomipramine hydrochloride, desipramine hydrochloride, imipramine hydrochloride, doxepin hydrochloride, carbamazepine, cyclobenzaprine hydrochloride, amoxapine hydrochloride, maprotiline hydrochloride, trimipramine maleate, and protriptyline hydrochloride.

At least 10 days should elapse between the discontinuation of another MAO inhibitor and the institution of phenelzine sulfate.

MAO inhibitors, including phenelzine sulfate, potentiate hexobarbital hypnosis in animals. Therefore, barbiturates should be given at a reduced dose with phenelzine sulfate.

MAO inhibitors inhibit the destruction of serotonin and noradrenaline, which are believed to be released from tissue stores by rauwolfia alkaloids. Accordingly, caution should be exercised when rauwolfia is used concomitantly with an MAO inhibitor, including phenelzine sulfate. Phenelzine sulfate 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 phenelzine sulfate and the institution of another antidepressant or buspirone hydrochloride.

There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when serotonin re-uptake inhibitors or venlafaxine hydrochloride has been combined with an MAO inhibitor. Therefore, phenelzine sulfate should not be used in combination with venlafaxine hydrochloride, or serotonin re-uptake inhibitors.

Before initiating phenelzine sulfate after using other serotonin re-uptake inhibitors, a sufficient amount of time must be allowed for clearance of the serotonin re-uptake inhibitor and its active metabolites. Allow at least five weeks between discontinuation of fluoxetine and initiation of phenelzine sulfate and at least 10 days between discontinuation of phenelzine sulfate and initiation of fluoxetine, or other serotonin re-uptake inhibitors.

The combination of MAO inhibitors and tryptophan has been reported to cause behavioral and neurological symptoms including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperflexia, shivering, ocular oscillations and Babinski signs.

4.6 Fertility, pregnancy and lactation

Pregnancy

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The safe use of phenelzine sulfate during pregnancy has not been established. There are insufficient adequate and well-controlled studies in pregnant women. Therefore, phenelzine should be used in pregnant women only if clearly needed and if the potential benefits justify the potential risk to the fetus.

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 medicine 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.

Breast-feeding

The safe use of phenelzine sulfate during lactation has not been established. There are insufficient adequate and well-controlled studies in lactating women. Therefore, phenelzine sulfate should be used in lactating women only if clearly needed. It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants to phenelzine sulfate, a decision should be made whether to discontinue the medicine, taking into account the importance of the medicine to the mother, or to discontinue nursing.

Fertility

25 female white mice were given 25 mg/kg per day phenelzine sulfate by s.c. injection on days 1-6 of pregnancy. The first day of pregnancy was dated from the finding of the vaginal plug. 9 out of 25 (36%) mice had surviving litters at autopsy on day 14, the remaining sixteen showed no signs of implantation. Within the control group, 67% of mice with vaginal plugs became pregnant. This result was statistically significant ($p < 0.001$). It was concluded that, during the first 6 days of gestation, implantation was partially suppressed.

4.7 [Effects on ability to drive and use machines](#)

Produces adverse effects on driving ability.

4.8 [Undesirable effects](#)

Phenelzine sulfate is a potent inhibitor of monoamine oxidase. Because this enzyme is widely distributed throughout the body, diverse pharmacological effects can be expected to occur. When they occur, such adverse effects can be mild, moderate or severe (see below), and can be minimised by adjusting dosage.

Common side effects include:

Nervous System: Dizziness, headache, drowsiness, sleep disturbances (including insomnia and hypersomnia), fatigue, weakness, tremors, twitching, myoclonic movements, hyperreflexia.

Gastrointestinal: Constipation, dry mouth, gastrointestinal disturbances, elevated serum transaminases (without accompanying signs and symptoms).

Metabolic: Weight gain.

Cardiovascular: Postural hypotension, oedema.

Genitourinary: Sexual disturbances, i.e., anorgasmia and ejaculatory disturbances.

Special Senses: Blurred vision.

Less common mild to moderate side effects (some of which have been reported in a single patient or by a single physician) include:

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Nervous System: Jitteriness, nervousness, palilalia, euphoria, nystagmus, paraesthesias, confusion, hallucinations, behavioural changes.

Genitourinary: Urinary retention.

Metabolic: Hypernatraemia.

Haematological: Blood dyscrasias.

Cardiovascular: Arrhythmias.

Dermatological: Pruritus, skin rash, sweating.

Special Senses: Glaucoma.

Of the more severe side effects that have been reported with any consistency, hypomania has been the most common. This reaction has been largely limited to patients in whom disorders characterised by hyperkinetic symptoms coexist with, but are obscured by, depressive affect; hypomania usually appeared as depression improved. If agitation is present, it may be increased with phenelzine sulfate. Hypomania and agitation also have been reported at higher than recommended doses, or following long-term therapy.

Although reported less frequently, and sometimes only once, additional severe side effects include:

Nervous System: Ataxia, shock-like coma, toxic delirium, manic reaction, delusional parasitosis, convulsions, acute anxiety reaction, precipitation of schizophrenia, acute dystonic reaction, sensorimotor peripheral neuropathy, speech blockade, transient respiratory and cardiovascular depression following ECT, neuroleptic malignant syndrome (occasionally fatal).

Gastrointestinal: To date, fatal progressive necrotising hepatocellular damage has been reported infrequently. Reversible jaundice.

Haematological: Leucopenia.

Immunological: Lupus-like illness.

Metabolic: Inappropriate ADH secretion, Hypermetabolic syndrome (which may include, but is not limited to, hyperpyrexia, tachycardia, tachypnoea, muscular rigidity, elevated CK levels, metabolic acidosis, hypoxia, coma and may resemble an overdose).

Respiratory: Oedema of the glottis.

General: Fever associated with increased muscle tone.

The most serious reactions to phenelzine sulfate involve changes in blood pressure.

Hypertensive Crises

The most important reaction associated with phenelzine sulfate administration is the occurrence of hypertensive crises, which have sometimes been fatal.

These crises are characterised by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain.

NOTE: Intracranial bleeding has been reported in association with the increase in blood pressure.

Blood pressure should be observed frequently to detect evidence of any pressor response in all patients receiving phenelzine sulfate. Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during therapy.

Recommended treatment in hypertensive crisis

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If a hypertensive crisis occurs, phenelzine sulfate should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. On the basis of present evidence, phentolamine is recommended (The dosage reported for phentolamine is 5 mg intravenously). Care should be taken to administer this medicine slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling.

Withdrawal may be associated with nausea, vomiting, and malaise.

An uncommon withdrawal syndrome following abrupt withdrawal of phenelzine sulfate has been infrequently reported. Signs and symptoms of this syndrome generally commence 24 to 72 hours after medicine discontinuation and may range from vivid nightmares with agitation to frank psychosis and convulsions. This syndrome generally responds to reinstatement of low-dose phenelzine sulfate therapy followed by cautious downward titration and discontinuation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>.

4.9 Overdose

Note - For management of Hypertensive Crisis see section 4.8. Accidental or intentional overdosage may be more common in patients who are depressed. It should be remembered that multiple medicines and/or alcohol may have been ingested.

Depending on the amount of overdosage with phenelzine sulfate, a varying and mixed clinical picture may develop, including signs and symptoms of central nervous system and cardiovascular stimulation and/or depression. Signs and symptoms may be absent or minimal during the initial 12- hour period following ingestion and may develop slowly thereafter, reaching a maximum in 24-48 hours. Death has been reported following overdosage. Therefore, immediate hospitalisation with continuous patient observation and monitoring throughout this period, is essential.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, rigidity, convulsions and coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Treatment

Intensive symptomatic and supportive treatment may be required. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids. Vasopressors are best avoided. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

There are no data on the lethal dose in man. The pathophysiological effects of massive overdosage may persist for several days, since the medicine acts by inhibiting physiological enzyme systems.

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With symptomatic and supportive measures, recovery from mild overdosage may be expected within 3 to 4 days. Haemodialysis, peritoneal dialysis, and charcoal haemoperfusion may be of value in massive overdosage, but sufficient data are not available to recommend their routine use in these cases.

Toxic blood levels of phenelzine have not been established, and assay methods are not practical for clinical or toxicological use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, monoamine oxidase inhibitors, nonselective: ATC code: N06AF03.

Mechanism of action

MAO is a complex flavin-containing enzyme system that is widely distributed throughout the body. MAO inhibitors exert their effects mainly on organ systems influenced by sympathomimetic amines and 5-hydroxytryptamine and inhibit not only MAO but also other enzymes as well, interfering with the hepatic metabolism of many medicines. It is unknown whether all the clinical effects produced by this class of medicine result from MAO inhibition, other pharmacological actions, or an interaction of both. Therefore the physician should become familiar with all the effects produced by medicines of this class.

Phenelzine sulfate is oxidised by MAO to form reactive intermediates which then irreversibly inactivate the flavin prosthetic group of MAO. In the clinical setting, maximal inhibition of MAO is usually achieved within a few days (5 to 10 days in biopsy samples), although the antidepressant effect may be delayed for 2 to 3 weeks. Evaluation of MAO activity in human subjects indicates that favourable clinical responses are likely to occur when platelet MAO is inhibited by 85%.

Up to 2 weeks may be required to restore amine metabolism to normal following withdrawal of MAO inhibitors, presumably because of the necessity for the re-synthesis of MAO. This is the reason why a period of 10 to 14 days is necessary after discontinuing MAO therapy before commencing a normal diet (see section 4.4).

5.2 Pharmacokinetic properties

There is little information available on the pharmacokinetics of phenelzine sulfate. Orally administered phenelzine sulfate is rapidly absorbed from the gastro-intestinal tract and has a short half-life reported to be 1.2 hours in humans. The decay in the action-time curve for MAO inhibitors is not dependent on the pharmacokinetic parameters but on the rate of protein synthesis which restores the functional levels of MAO in the tissue compartments where it has been irreversibly inactivated. Although the biological activity of phenelzine sulfate is prolonged due to the characteristics of their interaction with the enzyme, its clinical efficacy appears to be reduced when given less frequently than once daily. Phenelzine sulfate is metabolised primarily by acetylation. The rate of metabolism is dependent upon the kinetic profile of the patient who may be a "slow" or "rapid" acetylator. There has been no consistent correlation noted between acetylator status and adverse effects of the medicine. The major metabolites of phenelzine sulfate are phenylacetic acid and parahydroxyphenyl acetic acid. These metabolites constitute up to 79% of a single administered phenelzine dose excreted in the urine within 96 hours. It is not known whether these metabolites have clinical activity.

5.3 Preclinical safety data

Carcinogenicity and Mutagenicity

Carcinogenicity has been observed in mouse studies but not in the rat. This is consistent with tumour and mutagenicity data reported for the MAO inhibitor, isoniazid.

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A group of 50 male and 50 female random-bred Swiss mice, 6 weeks of age, were given 0.015% phenelzine sulfate in the drinking water for their lifetime. An untreated group of 200 mice served as controls. Of the treated group, pulmonary tumours developed as follows: 38% adenomas, 7% adenomas and adenocarcinomas, and 1% adenocarcinomas). This compared to the pulmonary tumour incidence in the untreated group of 14% adenomas, 3% adenomas and adenocarcinomas, and 5% adenocarcinomas. Of the mice in the treated group 26% developed vascular tumours compared to 5% in the untreated group.

An 87 week study of 26 male Sprague-Dawley rats, fed diets of phenelzine to evaluate carcinogenesis reported no significant difference in the incidence of both colonic and small intestinal adenocarcinomas between the phenelzine treated group (n=13) and matched controls (n=13).

In the Salmonella typhimurium DNA reversion (Ames) test, phenelzine sulfate was a weak inducer of base-pair mutations in the absence of metabolic activation by rat liver homogenate. Results obtained in the pol A+/A- DNA reversion test in Escherichia coli report phenelzine sulfate as reactive against DNA. Similarly, phenelzine sulfate has been reported to inactivate Bacillus subtilis plasmid DNA.

There is insufficient evidence to assess the carcinogenicity of phenelzine sulfate in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients include mannitol, povidone, starch-maize, magnesium stearate, and OPADRY AMB II High Performance Moisture Barrier Film Coating 88A250030 Orange.

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze).

6.5 Nature and contents of container

Tablets, 15 mg (orange), 100 tablets. Contained within a white, high density polyethylene (HDPE) bottle fitted with a child resistant white polypropylene (PP) cap with an induction heat sealed liner.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Neon Healthcare Ltd.
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15 Customs Street West
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9. DATE OF FIRST APPROVAL

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15 December 2005

10. DATE OF REVISION OF THE TEXT

02 September 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3	Description of tablet included.
6.1	Change in tablet composition.
6.3	Shelf life updated to 24 months.
6.5	Minor change in the cap of the container, adding an induction heat sealed liner.