SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nardil Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Phenelzine Sulphate BP equivalent to phenelzine base 15mg.

3 PHARMACEUTICAL FORM

Film coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenelzine is a monoamine oxidase inhibitor (MAOI). It has been found to be effective in depressed patients clinically characterised as ‘atypical’, ‘non endogenous’, ‘neurotic’ or where treatment with other antidepressants has failed. These patients often have mixed anxiety and depression and phobic or hypochondriacal features. There is less conclusive evidence of its usefulness with severely depressed patients with endogenous features.

4.2 Posology and method of administration

Oral Administration.

Adults:
One 15mg tablet three times a day. A response is usually seen within the first week. If no response is evident after two weeks, the dosage may be increased to a maximum of one 15mg tablet four times a day. Doses of up to two 15mg tablets three times a day may be used in hospitals. The effectiveness of the drug may not become apparent in less than 4 weeks therapy. After a satisfactory response has been achieved, the dosage may be reduced very gradually to a suitable maintenance level. This may be as low as one 15mg tablet every other day.

Elderly (over 65 years):

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.

Despite these problems, MAOIs (including Nardil) have been found to be useful in the treatment of depression in the elderly.

Children:

Nardil is not indicated for children under 16 years of age.

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4.3 Contraindications

Nardil should not be used in patients who are 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. Phenelzine sulphate 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 phenelzine therapy. It is recognised that there is some division of consultant opinion with respect to concomitant use of MAOIs and tricyclic antidepressants.

There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when serotonin reuptake inhibitors or serotonin/noradrenaline inhibitors (eg. venlafaxine) have been combined with MAOIs. Therefore, Nardil should not be used in combination with these drugs and before initiating Nardil, a sufficient amount of time must be allowed for clearance of the drugs and its metabolites. 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 phenelzine. Phenelzine sulphate 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.

Phenelzine is not indicated in manic phase.

4.4 Special warnings and precautions for use

Nardil should be withdrawn two weeks before elective surgery/dentistry.

Nardil should not be given with cocaine or local anaesthesia containing sympathomimetic vasoconstrictors and the possible combined hypotensive effects of Nardil and spinal anaesthesia should be kept in mind.
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.

Nardil should only be used with great caution in agitated patients or these who have cardiovascular disease, epilepsy, blood dyscrasias, porphyria or diabetes; and in patients taking diuretics.

Blood pressure should be observed frequently to detect any pressor response and therapy discontinued if palpitations or frequent headaches occur.

Patients should also be closely followed for symptoms of postural hypotension. Hypotensive side effects have occurred in hypertensive as well as normotensive and hypotensive patients.

Due to the possibility of patients undergoing “Withdrawal Syndrome” (see section 4.8 Undesirable Effects) abrupt withdrawal of phenelzine should be avoided where possible.

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Patients should be warned against self medication, particularly cold cures, cough cures, hay fever medications, anti-appetite medicines, weight reducing preparations and “pep” pills and about potential food interactions.

Patients under treatment with Nardil should avoid high protein food that has undergone breakdown by aging, 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 Nardil and certain foodstuffs occurs the intensity of the reaction is usually related to the tyramine content of the food. The reaction is now well recognised and serious hypertensive episodes are extremely rare. Should such a reaction occur, the hypertension should be controlled promptly by slow administration of phentolamine 5-10mg I.V. repeated if necessary. Care should be taken to administer this drug slowly to avoid an excessive hypotensive effect.

Nardil may also potentiate the effects of alcohol.

Nardil may potentiate the action of pethidine, morphine, adrenaline, amphetamines and other sympathomimetic amines such as fenfluramine, ephedrine, phenylpropanolamine, dopamine and levodopa (see also Contraindications). Nardil may also potentiate the effects of antihypertensives, hypoglycaemic agents, sympathomimetics, anti-Parkinson drugs, antimuscarnics, 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 amfebutanone (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

Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons. There is no evidence as to drug safety in human pregnancy nor is there evidence from animal work that it is free from hazard.
It is not known if phenelzine is excreted in breast milk. Because of the potential for serious adverse effects to the infant, a decision should be made whether to discontinue the drug or not to breast feed.

### 4.7 Effects on ability to drive and use machines

Produces adverse effects on driving ability.

### 4.8 Undesirable effects

Side-effects tend to be mild or moderate in severity, often subsiding as treatment continues, and can be minimised by adjusting dosage; rarely is it necessary to discontinue Nardil.

The most important reaction associated with Nardil is the occurrence of hypertensive crises, which have been associated with intracranial bleeding and have sometimes been fatal.

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

Common side-effects include: dizziness, drowsiness, weakness and fatigue, oedema, gastro-intestinal disturbances (nausea, vomiting, dryness of the mouth, constipation), insomnia, blurred vision, adverse effects on 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, pruritus, 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 side-effects have been reported very rarely, including isolated reports in some cases. These 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 necrotising hepatocellular damage, reversible jaundice, hypermetabolic syndrome, oedema of the glottis and fever associated with increased muscle tone.

Hyponatraemia (usually in the elderly and possibly 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 Nardil has been infrequently reported. Signs and symptoms of this syndrome generally commence 24 to 72 hours after drug discontinuation and may vary from vivid nightmares and agitation to frank psychosis and convulsions. This syndrome generally responds to reinstitution of low-dose Nardil therapy followed by cautious downward titration and discontinuation.

**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 Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

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 to 48 hours. Death has been reported following overdosage. Therefore immediate hospitalisation with continuous patient observation and monitoring throughout this period is essential.

Large doses may produce hypomania, euphoria, followed by coma with hypotension, or acute hypertension sometimes with subarachnoid haemorrhage. In a few cases extra-pyramidal symptoms have been recorded.

Other symptoms may be: 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:**

Gastric lavage with instillation of charcoal slurry may be helpful in early poisoning (tablets dissolve slowly in stomach).

Absolute bed rest, raise feet in hypotension. Vasopressors are best avoided. Hypertension should be urgently controlled with phentolamine I.V. Avoid hypnotics, such as morphine, pethidine, barbituates. Body temperature should be monitored, and fever managed by cooling.

Use intravenous therapy to maintain fluid and electrolyte balance and use a slow I.V. injection of diazepam for any CNS stimulation. In deep coma and severe hypotension hydrocortisone by injection may be tried.

There is no specific antidote for Nardil. 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.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The MAO inhibitors comprise a chemically heterogeneous group of drugs that have in common the ability to block oxidative deamination of naturally occurring monoamines.

MAO inhibitors exert their effects mainly in organ systems influenced by sympathomimetic amines and 5-HT.

The MAO inhibitors in clinical use are site-directed irreversible inhibitors. The hydrazines attack and inactivate the flavin prosthetic group following their oxidation to reactive intermediates by MAO.

The capacity of MAO inhibitors to act as antidepressants has most often been assumed to reflect the increased availability of one or more monoamines in the CNS or sympathetic nervous system.

5.2 Pharmacokinetic properties

All the currently employed MAO inhibitors are readily absorbed when given by mouth. These drugs produce maximal inhibition of MAO in biopsy samples from man within 5 to 10 days. There is little information on their pharmacokinetics. However, their biological activity is prolonged due to the characteristics of their interactions with the enzyme.

The hydrazide MAO inhibitors are thought to be cleaved with resultant liberation of active products. They are inactivated primarily by acetylation.

5.3 Preclinical safety data

There are no pre-clinical safety data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets also contain mannitol, povidone, magnesium stearate and maize starch. The tablet coating contains hydroxypropyl cellulose, polyvinylacetatephthalate, stearic acid, sunset yellow (E110), titanium dioxide (E171), erythrosine (E127) hydroxypropylmethylcellulose (E464) and talc.

6.2 Incompatibilities

None known.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store between 2°C to 8°C in a refrigerator, unless unavoidable for short periods.

6.5 Nature and contents of container

White, high density polyethylene bottle fitted with a white, high density, polyethylene child resistant, tamper evident cap with expanded polyethylene liner, containing 100 tablets.

6.6 Special precautions for disposal

No special requirements.
7 MARKETING AUTHORISATION HOLDER

Kyowa Kirin Limited
Galabank Business Park
Galashiels
TD1 1QH
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16508/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/07/1999

10 DATE OF REVISION OF THE TEXT

01/03/2017