EMERGENCY MEDICAL TREATMENT PROTOCOL
FOR
ACCIDENTAL EXPOSURE TO MPTP

1. Remove any contaminated clothing.

2. Rinse any contaminated skin surfaces copiously with water.

3. Have the exposed employee take **6 (six) 5 mg. tablets of Selegiline (Eldepryl) by mouth** as soon as possible.*

4. Exposed employee should report or be transported to the Boston Medical Center Emergency Department at East Newton Campus (617–638–6420).

   It is important that the exposed employee not drive him or herself at this time due to the potential for hypotension (low blood pressure) from Selegiline. Should the exposed employee lose consciousness prior to transport, place them on the floor on their back and elevate their legs. Do not attempt to transport an unconscious person but call Security at (638–4444) to arrange transport to the emergency room by ambulance.

* It is the responsibility of the Principal Investigator to make sure that a supply of Selegiline be available to all researchers with potential exposure to MPTP in his/her laboratory. It is the responsibility of the Principal Investigator to reorder Selegiline prior to the expiration date from a physician at the Boston Medical Center Occupational & Environmental Medicine Department.

POTENTIAL FOOD AND DRUG INTERACTIONS WITH SELEGILINE (ELDEPRYL)[1]

Selegiline (Eldepryl) potentially interacts with many foods, prescription drugs, and non-prescription drugs with serious and sometimes **fatal** consequences. Selegiline is a member of a class of drugs known as monoamine oxidase inhibitors (MAOIs). Hypertensive crises may occur when patients taking MAOIs consume foods that contain large amounts of tyramine and tryptophan. Agents that selectively inhibit monoamine oxidase type B (such as Selegiline) are **theoretically** less likely to cause hypertensive crises than agents that nonselectively inhibit MAO. However, caution is recommended for all patients, especially when higher than recommended doses are prescribed, as for treatment for MPTP exposure. When Selegiline is used in high doses, it is recommended that the patient avoid the following foods:

(Contraindicated foods while working with MPTP starting 24 hours prior to working with MPTP)

Cheese (particularly strong, aged, or processed cheeses)
Sour cream
Wine (particularly red wine)
Champagne
Beer
Herring
Anchovies
Caviar
Shrimp paste
Liver (particularly chicken liver)
Sausage
Figs
Raisins
Bananas
Avocados
Chocolate
Soy sauce
Bean curd
Yogurt
Papaya products
Meat tenderizers (e.g., Adolphs)
Fava beans
Protein extracts

Dietary supplements.

Caffeine may also precipitate hypertensive crises and should be avoided.

CONTRAINDICATED MEDICATIONS WITH SELEGILINE (ELDEPRYL)

Numerous prescription and over the counter medications may interact with Selegiline. Be sure to discuss any medications that you are currently taking with the physician who screens you to work with MPTP and **DO NOT BEGIN ANY MEDICATIONS** without first consulting the physician.

Tricyclic antidepressants: Dibenzazepine Derivative Drugs by generic name follows**:**

Pamelor (nortriptyline hydrochloride)
Elavil (amitriptyline hydrochloride)
(perphenazine and amitriptyline hydrochloride)
(clomipramine hydrochloride)
Norpramin(desipramine hydrochloride)
(imipramine hydrochloride)
Sinequan(doxepin)
Tegretol (carbamazepine)
Flexeril (cyclobenzaprine HCl)
Asendin (amoxapine)
maprotiline HCl
Surmontil (trimipremine maleate)
Vivacil (protriptyline HCl)
Remeron (mirtazapine)

Ephedrine containing medications

MAO Inhibitors:

Nardil (phenelzine sulfate)
Parnate (pargyline hydrochloride)
Furoxone(furazolidone)
(isocarboxazid)
(procarbazine)
(tranylcypromine)
BuSpar (buspirone HCl)

Opioids: including Demerol (meperidine)

Serotonergic Drugs:

Prozac (fluoxetine hydrochloride)
Paxil (paroxetine)
dexfenfluraine
Luvox (fluvoxmine)
Zoloft (sertraline)
Effexor (venlafaxine)

Antihypertensive drugs including thiazide diuretics (methylclothiazide)

and beta blockers

Over–the Counter Medication to Avoid

Cold and cough preparations (including those containing Dextromethorphan)
Nasal decongestants (tablets, drops, or sprays)
Hay–fever medications
Sinus medications
Asthma inhalant medications
Anti–appetite medications
Weight-reducing preparations
"Pep" pills
L–tryptophan containing preparations

REMEMBER! As soon as you begin working with MPTP you will be at risk for taking Selegiline at any time. The above food restrictions should begin at least 24 hours prior to beginning work with MPTP and need to be continued until your risk of exposure is over. If you have been taking certain medications, these medications must be restricted prior to working with MPTP for up to several weeks prior to working with MPTP depending on the specific medication. You must continue to avoid medications that are contraindicated with Selegiline until your risk of exposure is over.

It is important for the person who will be at risk of exposure to MPTP to know that there is no human clinical experience regarding attempts to treat acute exposure to MPTP with MAOIs and that the theoretical benefit of such attempts is based on data from animal experimentation.

If you have questions about any medication you are taking, prescription or over the counter with regard to its potential interaction with Selegiline, you must contact Cheryl Barbanel, MD, at BMC Occupational & Environmental Medicine (617–638–8410) or a neurologist in the movement disorder clinic (617–638–8456) prior to working with MPTP. See Appendix A.

Risks and Precautions to take when working with MPTP have been reviewed with me and I have been given a copy of the MPTP medical surveillance protocol.

_____ _____

Signature of Researcher Date

_____

Clinician

PROTOCOL FOR MEDICAL EVALUATION OF A WORKER EXPOSED TO MPTP

MPTP (methyl–phenyl –tetrahydro-pyridine) and its analogs are neurotoxins used in animal models to simulate Parkinson's syndrome. Low dose exposures may cause **irreversible** neurologic damage to dopamine neurons. A percutaneous exposure to MPTP is a genuine emergency. Immediate treatment with a MAOI may prevent the conversion of MPTP to its toxic metabolites. This recommendation is based on animal data only. There has been no human clinical experience documenting the benefit of this use of MAOIs.

1. Contact the Boston Medical Center Emergency Department on the East Newton Campus at (638–6420) to report the exposure prior to the arrival or transporting of the exposed employee (patient), if possible.

2. If 6 (six) 5mg. tablets of Selegiline (Eldepryl) have not been administered by mouth at the time the call is received at the BMC OEM, instruct the employee to do this at once. (The medication is to be available on site.)

3. If the patient is ambulatory have the patient report to the BMC Emergency Department (ED). **The patient is NOT to drive him or herself at this time!** If the patient is not ambulatory call Security at 638–4444 to arrange transport by ambulance for patient to the BMC ED. Take this Protocol with the patient and provide it to the attending physician. The remaining Selegiline (Eldepryl) (Deprenyl) should be carried with the patient to the ED.

4. The attending physician obtains a brief medical history, including an estimate of the amount of MPTP involved.

5. The attending physician performs a focused physical exam of the injury site and then performs a thorough neurological exam noting any evidence of tremors, motor weakness, or rigidity. Temperature, respiratory rate, pulse, and blood pressure are obtained including postural readings of pulse and blood pressure in the supine, sitting, and standing positions. Vital signs should be monitored for 2 hours.

6. The attending physician contacts the Movement Disorder Clinic Physician through the on call neurologist at 617–638–8456. (Appendix A^3: Movement Disorder Physicians)

7. The patient is instructed to take 3 (three) 5 mg. tablets of Selegiline twice a day for the next 3 (three) days.

8. The potential adverse reactions of Selegiline are reviewed with the patient, as are the dietary and medication precautions to be taken. It is important to remind the

patient that dietary precautions and drug restrictions need to be continued for 2 to 4 **weeks** after Selegiline is given in order to minimize the possibility of interaction.

9. The patient is reevaluated daily for the next 3 (three) days at the Movement Disorder Clinic.

[1] Appendix B: PDR on Eldepryl
[2] Appendix C: PDR on Nardil
[3] Appendix A: Important Contact Information

References:

1. Przedborski et al (2001) The parkinsonian toxin 1–methyl–4–phenyl–1,2,3,6-tetrahydropyridind (MPTP): a technical review of its utility and safety. J neurochem. Mar: 76(5):1265–74.
2. Personal Communication with Serge Przedborski at Columbia University.
3. Personal Communication with Dr. Michael Schwarzchild at MGH
4. PDR: Eldepryl Capsules, and Nardil
5. NIH Procedures for working with MPTP and animals
6. Monoamine Oxidase Inhibitors in Neurological Diseases, eds: Abraham Lieberman, C Warren Olanow, Moussa B H Youdim, Keith Tipton Marcel Dekker, Inc., New York, Basel, Hong Kong, 1994

The protocol is based on the NIH protocol. The committee adapted this protocol for BUMC. An ad hoc MPTP Committee was met on 10/18/02 and 12/17/02. The MPTP Committee reviewed current recommendations in the literature on medical surveillance for MPTP, current practices of investigators performing research with MPTP, and known information on the metabolism of Selegiline. The committee participants included, Neurologist, Marie St. Hilaire, MD, Dr. Mark Moss, PhD, Chairman of Neurobiology, Jiang-Fan Chen, MD, PhD, PI, working at BUSM with MPTP and Cheryl Barbanel, MD, MBA, MPH (Chair), Chief of Occupational Medicine at BMC.

Additional consultants included Robert Feldman, MD, Serge Przedborski, MD, PhD, Columbia University, Michael Schwarzschild, MD, PhD, MGH, and occupational medicine physician RonVoight, MD, at Care Group.

Appendix A

Important Contact Information

Movement Disorder Clinic 617–638–8456
BMC Department of Neurology

Marie St. Hilaire, MD
Samuel Ellias, MD
Peter Novak, MD

Security (617) 638–4444
Control (617) 638–4144
Environmental Health & Safety (617) 638–8830

BMC Occupational & Environmental Medicine 617–638–8400
Cheryl Barbanel, MD (617) 638–8410 or (617) 353–6630

This protocol was prepared by Cheryl Barbanel, MD, MBA, MPH. Please contact Dr. Barbanel, if information needs to be updated on this protocol or appendix at (617) 638–8410).

Appendix B

Physicians' Desk Reference Information on Selegiline (Eldepryl)

PHYSICIANS' DESK REFERENCE

PDR® entry for
Eldepryl Capsules (Somerset)

DESCRIPTION

ELDEPRYL (Selegiline hydrochloride) is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l-deprenyl.

The chemical name is: (R)-(-)- *N,2* -dimethyl- *N-2* -propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The structural formula is as follows:

Each aqua blue capsule is band imprinted with the Somerset logo on the cap and "Eldepryl 5 mg" on the body. Each capsule contains 5 mg Selegiline hydrochloride. Inactive ingredients are citric acid, lactose, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

The mechanisms accounting for Selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase (MAO), type B, activity is generally considered to be of primary importance; in addition, there is evidence that Selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety, which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because Selegiline has greater affinity for type B rather than for type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a `hypertensive crisis,' the so–called `cheese reaction.' (If large amounts of certain exogenous amines gain access to the systemic circulation – e.g., from fermented cheese, red wine, herring, over–the–counter cough/cold medications, etc. – they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

In theory, since MAO A of the gut is not inhibited, patients treated with Selegiline at a dose of 10 mg a day should be able to take medications containing pharmacologically active amines and consume tyramine–containing foods without risk of uncontrolled hypertension. Although rare, a few reports of hypertensive reactions have occurred in patients receiving Eldepryl at the recommended dose, with tyramine–containing foods. In addition, one case of hypertensive crisis has been reported in a patient taking the recommended dose of Selegiline and a sympathomimetic medication, ephedrine. The pathophysiology of the `cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, Selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons. However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that Selegiline can ordinarily only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day).

In short, attention to the dose dependent nature of Selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a few cases of hypertensive reactions have been reported at the recommended dose. (See WARNINGS and PRECAUTIONS .)

It is important to be aware that Selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re–uptake at the synapse. Effects resulting from Selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of Selegiline are unknown.

Rationale for the Use of a Selective Monoamine Oxidase Type B Inhibitor in Parkinson's Disease:
Many of the prominent symptoms of Parkinson's disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopami–nergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's Disease, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa).

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (i.e., there is `wearing off'), and is often accompanied by side effects (e.g., dyskinesia, akinesias, on–off phenomena, freezing, etc.).

This deteriorating response is currently interpreted as a manifestation of the inability of the ever–decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabolism of dopamine, it would increase the net amount of dopamine available (i.e., it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive Selegiline is unknown.

Selegiline's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non–selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement, and toxic delirium.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination--ADME):

The absolute bioavailability of Selegiline following oral dosing is not known; however, Selegiline undergoes extensive metabolism (presumably attributable to presystemic clearance in gut and liver). The major plasma metabolites are N–desmethylSelegiline, L–amphetamine and L–methamphetamine. Only N–desmethylSelegiline has MAO–B inhibiting activity. The peak plasma levels of these metabolites following a single oral dose of 10 mg are from 4 to almost 20 times greater than that of the maximum plasma concentration of Selegiline [1 ng/mL]. The maximum concentrations of amphetamine and methamphetamine, however, are far below those ordinarily expected to produce clinically important effects.

Single oral dose studies do not predict multiple dose kinetics, however. At steady state the peak plasma level of Selegiline is 4 fold that obtained following a single dose. Metabolite concentrations increase to a lesser extent, averaging 2 fold that seen after a single dose.

The bioavailability of Selegiline is increased 3 to 4 fold when it is taken with food.

The extent of systemic exposure to Selegiline at a given dose varies considerably among individuals. Estimates of systemic clearance of Selegiline are not available. Following a single oral dose, the mean elimination half–life of Selegiline is two hours. Under steady state conditions the elimination half-life increases to ten hours.

Because Selegiline's inhibition of MAO–B is irreversible, it is impossible to predict the extent of MAO-B inhibition from steady state plasma levels. For the same reason, it is not possible to predict the rate of recovery of MAO–B activity as a function of plasma levels. The recovery of MAO–B activity is a function of de novo protein synthesis; however, information about the rate of de novo protein synthesis is not yet available. Although platelet MAO–B activity returns to the normal range within 5 to 7 days of Selegiline discontinuation, the linkage between platelet and brain MAO–B inhibition is not fully understood nor is the relationship of MAO–B inhibition to the clinical effect established (see Clinical Pharmacology).

Special Populations:

Renal Impairment:

No pharmacokinetic information is available on Selegiline or its metabolites in renally impaired subjects.

Hepatic Impairment:

No pharmacokinetic information is available on Selegiline or its metabolites in hepatically impaired subjects.

Age:

Although a general conclusion about the effects of age on the pharmacokinetics of Selegiline is not warranted because of the size of the sample evaluated (12 subjects greater than 60 years of age, 12 subjects between the ages of 18 to 30), systemic exposure was about twice as great in older as compared to a younger population given a single oral dose of 10 mg.

Gender:

No information is available on the effects of gender on the pharmacokinetics of Selegiline.

INDICATIONS AND USAGE

ELDEPRYL is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that Selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added Selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of `off' time, and patient self–rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS

ELDEPRYL is contraindicated in patients with a known hypersensitivity to this drug.

ELDEPRYL is contraindicated for use with meperidine (DEMEROL & other trade names). This contraindication is often extended to other opioids. (See Drug Interactions.)

WARNINGS

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with nonselective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of Selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day. Rare cases of hypertensive reactions associated with ingestion of tyramine–containing foods have been reported in patients taking the recommended daily dose of Selegiline. The selectivity is further diminished with increasing daily doses. The precise dose at which Selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non–selective MAOIs (NARDIL, PARNATE). A similar reaction has been reported for a patient on amitriptyline and ELDEPRYL. Another patient receiving protriptyline and ELDEPRYL developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after ELDEPRYL was added. Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving ELDEPRYL and various tricyclic antidepressants.

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride (PROZAC) and non–selective MAOIs. Similar signs have been reported in some patients on the combination of ELDEPRYL (10 mg a day) and selective serotonin

reuptake inhibitors including fluoxetine, sertraline and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of ELDEPRYL and tricyclic antidepressants as well as ELDEPRYL and selective serotonin reuptake inhibitors. At least 14 days should elapse between discontinuation of ELDEPRYL and initiation of treatment with a tricyclic antidepressant or selective serotonin reuptake inhibitors. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with ELDEPRYL.

PRECAUTIONS

General:

Some patients given Selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reaction with super sensitive, post–synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe Selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with Selegiline. Consequently, the full spectrum of possible responses to Selegiline may not have been observed in pre–marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients:

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of Selegiline should be explained, and a brief description of the `cheese reaction' provided. Rare hypertensive reactions with Selegiline at recommended doses associated with dietary influences have been reported.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests:

No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions:

The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of Selegiline and meperidine. Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination (see **CONTRAINDICATIONS**). Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and ELDEPRYL and selective serotonin reuptake inhibitors and ELDEPRYL. (See **WARNINGS** for details). One case of hypertensive crisis has been reported in a patient taking the recommended doses of Selegiline and a sympathomimetic medication (ephedrine).

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Assessment of the carcinogenic potential of Selegiline in mice and rats is ongoing.

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in Salmonella typhimurium and in an *in vivo* chromosomal aberration assay. While these studies provide some reassurance that Selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations. No definitive *in vitro* chromosomal aberration or *in vitro* mammalian gene mutation assays have been performed.

The effect of Selegiline on fertility has not been adequately assessed.

Pregnancy:

Pregnancy Category C: No teratogenic effects were observed in a study of embryo–fetal development in Sprague–Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12 and 35 times the human therapeutic dose on a mg/m 2 basis. No teratogenic effects were observed in a study of embryo–fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m 2 basis; however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat study, there was a decrease in fetal body weight at the highest dose tested. In the rabbit study, increases in total resorptions and % post–implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri – and postnatal development study in Sprague–Dawley rats (oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m 2 basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated off–spring was not assessed.

There are no adequate and well–controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether Selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use:

The effects of Selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS

Introduction:

The number of patients who received Selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of Selegiline are available (e.g., literature reports, foreign post–marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of Selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In

prospective pre–marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with Selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris, and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness, and weight loss.

Experience with ELDEPRYL obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to Selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

Adverse Event	**Number of Patients Reporting Events**	
	Selegiline hydrochloride N=49	placebo N=50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1

The following events were reported once in either or both groups:

Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0

Hair Loss
0 1
Insomnia
1 1
Lethargy
1 0
Leg pain
1 0

Low back pain
1 0
Malaise
0 1
Palpitations
1 0
Urinary Retention
1 0
Weight Loss
1 0

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System:

Motor/Coordination/Extrapyramidal:

increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric:

hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation:

headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

Autonomic Nervous System:

dry mouth, blurred vision, sexual dysfunction.

Cardiovascular:

orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal:

nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

Genitourinary/Gynecologic/Endocrine:

slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

Skin and Appendages:

increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous:

asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports:

The following experiences were described in spontaneous post–marketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL.

CNS:

Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE

Selegiline:

No specific information is available about clinically significant overdoses with ELDEPRYL. However, experience gained during Selegiline's development reveals that some individuals exposed to doses of 600 mg of d,l–Selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by Selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine (PARNATE), isocarboxazide (MARPLAN), and phenelzine (NARDIL)].

Overdose with Non-Selective MAO Inhibition:

NOTE:

This section is provided for reference; it does not describe events that have actually been observed with Selegiline in overdose.

Characteristically, signs and symptoms of non–selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in

overdose, is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

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, opisthotonos, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions For Overdose:

NOTE:

Because there is no recorded experience with Selegiline overdose, the following suggestions are offered based upon the assumption that Selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. 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 and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. 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.

DOSAGE AND ADMINISTRATION

ELDEPRYL is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of ELDEPRYL is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of Selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to Selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued Selegiline therapy.

HOW SUPPLIED

ELDEPRYL capsules are available containing 5 mg of Selegiline hydrochloride. Each aqua blue capsule is band imprinted with the Somerset logo on the cap and "Eldepryl 5 mg" on the body.

They are available as:

NDC 39506-022-60 bottles of 60 capsules.

NDC 39506-022-30 bottles of 300 capsules.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

Rx only

SOMERSET

PHARMACEUTICALS, INC .

Tampa, FL 33607

Literature issued July 1998

ELD:R16C

PRODUCT PHOTO(S):
NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.

CSB 1/2/03

Appendix C

Physicians' Desk Reference Information on NARDIL

SELEGILINE (ELDEPRYL) MAY ACT AS A NON-SLECTIVE MAO INHIBITOR AT HIGH DOSES THEREFORE INFORMATION ON NARDIL IS PROVIDED AS IT IS A PROTOTYPE FOR NON-SELECTIVE MAO INHIBITORS.

INFORMATION ON NON-SELECTIVE MAO INHIBITORS ARE CONTAINED IN THE PDR LISTING FOR NARDIL ATTACHED BELOW:

PHYSICIANS' DESK REFERENCE

PDR® entry for
Nardil Tablets (Parke–Davis)

DESCRIPTION

Nardil® (phenelzine sulfate) is a potent inhibitor of monoamine oxidase (MAO). Phenelzine sulfate is a hydrazine derivative. It is a molecular weight of 234.27 and is chemically described as C 8 H 12 N 2 ·N 2 SO 4. Its chemical structure is shown below:

Molecular weight: 234.27

Each Nardil tablet for oral administration contains phenelzine sulfate equivalent to 15 mg of phenelzine base. Inactive ingredients include: acacia NF; calcium carbonate; carnauba wax, NF; corn-starch, NF; FD and C yellow No. 6; gelatin, NF; kaolin, USP; magnesium stearate, NF; mannitol, USP; pharmaceutical glaze, NF; povidone, USP; sucrose, NF; talc, USP; white wax, NF; white wheat flour.

CLINICAL PHARMACOLOGY

Monoamine oxidase is a complex enzyme system, widely distributed throughout the body. Drugs that inhibit monoamine oxidase in the laboratory are associated with a number of clinical effects. Thus, it is unknown whether MAO inhibition per se, other pharmacologic actions, or an interaction of both is responsible for the clinical effects observed. Therefore, the physician should become familiar with all the effects produced by drugs of this class.

INDICATIONS AND USAGE

Nardil has been found to be effective in depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic." 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.

Nardil should rarely be the first antidepressant drug used. Rather, it is more suitable for use with patients who have failed to respond to the drugs more commonly used for these conditions.

CONTRAINDICATIONS

Nardil should not be used in patients who are hypersensitive to the drug or its ingredients, with pheochromocytoma, congestive heart failure, a history of liver disease, or abnormal liver function tests.

The potentiation of sympathomimetic substances and related compounds by MAO inhibitors may result in hypertensive crises (see WARNINGS). Therefore, patients being treated with Nardil should not take sympathomimetic drugs (including amphetamines, cocaine, methylphenidate, dopamine, epinephrine and norepinephrine) or related compounds (including methyldopa, L–dopa, L–tryptophan, L–tyrosine, and phenylalanine). Hypertensive crises during Nardil therapy may also be caused by the ingestion of foods with a high concentration of tyramine or dopamine. Therefore, patients being treated with Nardil should avoid high protein food that has undergone protein breakdown by aging, fermentation, pickling, smoking, or bacterial contamination. Patients should also 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 yogurt. Excessive amounts of caffeine and chocolate may also cause hypertensive reactions.

Nardil should not be used in combination with dextromethorphan or with CNS depressants such as alcohol and certain narcotics. Excitation, seizures, delirium, hyperpyrexia, circulatory collapse, coma, and death have been reported in patients receiving MAOI therapy who have been given a single dose of meperidine. Nardil should not be administered together with or in rapid succession to other MAO inhibitors because HYPERTENSIVE CRISES and convulsive seizures, fever, marked sweating, excitation, delirium, tremor, coma, and circulatory collapse may occur.

A List of MAO Inhibitors by generic name follows:

pargyline hydrochloride

pargyline hydrochloride
and methylclothiazide

furazolidone

isocarboxazid

procarbazine

tranylcypromine

Nardil should also not be used in combination with buspirone HCl, since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCl. At least 10 days should elapse between the discontinuation of Nardil and the institution of another antidepressant or buspirone HCl, or the discontinuation of another MAO inhibitor and the institution of Nardil.

There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when serotoninergic drugs (e.g., dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine) have been combined with an MAO inhibitor. Therefore the concomitant use of Nardil with serotoninergic agents is contraindicated (see PRECAUTIONS -- *Drug Interactions*). Allow at least five weeks between discontinuation of fluoxetine and initiation of Nardil and at least 10 days between discontinuation of Nardil and initiation of fluoxetine, or other serotoninergic agents. Before initiating Nardil after using other serotoninergic agents, a sufficient amount of time must be allowed for clearance of the serotoninergic agent and its active metabolites.

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

The concurrent administration of an MAO inhibitor and bupropion hydrochloride (Wellbutrin®) is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride.

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

MAO inhibitors, including Nardil, are contraindicated in patients receiving guanethidine.

WARNINGS

The most serious reactions to Nardil involve changes in blood pressure.

Hypertensive Crises: The most important reaction associated with Nardil administration is the occurrence of hypertensive crises, which have sometimes been fatal.

These crises are characterized 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 Nardil. Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during therapy.

Recommended treatment in hypertensive crisis: If a hypertensive crisis occurs, Nardil 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 drug slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling.

Warning to the Patient: All patients should be warned that the following foods, beverages, and medications must be avoided while taking Nardil, 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)

Sauerkraut

Dairy Products

Cheese (cottage cheese and cream cheese are allowed)

Yogurt

Beverages

Beer and 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 chocolate and caffeine

Also, 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 flavor should be avoided.

OTC 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

L–tryptophan containing preparations

Also, certain prescription drugs should be avoided. Therefore, patients under the care of another physician or dentist should inform him/her they are taking Nardil.

Patients should be warned that the use of the above foods, beverages, or medications may cause a reaction characterized 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 meperidine. Also, there has been a report of an interaction between Nardil and dextromethorphan (ingested as a lozenge) causing drowsiness and bizarre behavior.

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

Concomitant Use with Dibenzazepine Derivative Drugs

If the decision is made to administer Nardil concurrently with other antidepressant drugs, or within less than 10 days after discontinuation of antidepressant therapy, the patient should be cautioned by the physician regarding the possibility of adverse drug interaction.

A List of Dibenzazepine Derivative Drugs by generic name follows:

nortriptyline hydrochloride

amitriptyline hydrochloride

amitriptyline hydrochloride

perphenazine and amitriptyline hydrochloride

perphenazine and amitriptyline hydrochloride

clomipramine hydrochloride

desipramine hydrochloride

desipramine hydrochloride

imipramine hydrochloride

doxepin

doxepin

carbamazepine

cyclobenzaprine HCl

amoxapine

maprotiline HCl

trimipremine maleate

protriptyline HCl

mirtazapine

Nardil should be used with caution in combination with antihypertensive drugs, including thiazide diuretics and **(beta) –** blockers, since exaggerated hypotensive effects may result.

Use in Pregnancy: The safe use of Nardil during pregnancy or lactation has not been established. The potential benefit of this drug, if used during pregnancy, lactation, or in women of childbearing age, should be weighed against the possible hazard to the mother or fetus.

Doses of Nardil in pregnant mice well exceeding the maximum recommended human dose have caused a significant decrease in the number of viable offspring per mouse. In addition, the growth of young dogs and rats has been retarded by doses exceeding the maximum human dose.

Use in Pediatric Patients: Nardil is not recommended for pediatric patients under 16 years of age, since there are no controlled studies of safety in this age group. Nardil, as with other hydrazine derivatives, has been reported to induce pulmonary and vascular tumors in an uncontrolled lifetime study in mice.

PRECAUTIONS

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

All patients undergoing treatment with Nardil 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 pretreatment levels rapidly when the drug is discontinued or the dosage is reduced.

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

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 characterized 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 Nardil. Hypomania and agitation have also been reported at higher than recommended doses or following long–term therapy.

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

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

MAO inhibitors inhibit the destruction of serotonin and norepinephrine, 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 Nardil.

There is conflicting evidence as to whether or not MAO inhibitors affect glucose metabolism or potentiate hypoglycemic agents. This should be kept in mind if Nardil is administered to diabetics.

Drug Interactions

In patients receiving nonselective monoamine oxidase inhibitors (MAOIs)in combination with serotoninergic agents (e.g., dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafexine) there have been reports of serious, sometimes fatal, reactions. Because Nardil is a MAOI, Nardil should not be used concomitantly with a serotoninergic agent (See CONTRAINDICATIONS).

Geriatric Use

Clinical studies of Nardil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Nardil is a potent inhibitor of monoamine oxidase. Because this enzyme is widely distributed throughout the body, diverse pharmacologic effects can be expected to occur. When they occur, such effects tend to be mild or moderate in severity (see below), often subside as treatment continues, and can be minimized by adjusting dosage; rarely is it necessary to institute counteracting measures or to discontinue Nardil.

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, edema.

Genitourinary --Sexual disturbances, eg, anorgasmia and ejaculatory disturbances and impotence.

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

Nervous System --Jitteriness, palilalia, euphoria, nystagmus, paresthesias.

Genitourinary --Urinary retention.

Metabolic-- Hypernatremia.

Dermatologic --Pruritus, Skin rash, sweating.

Special Senses --Blurred vision, glaucoma.

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

Nervous System --Ataxia, shock-like coma, toxic delirium, manic reaction, convulsions, acute anxiety reaction, precipitation of schizophrenia, transient respiratory and cardiovascular depression following ECT.

Gastrointestinal --To date, fatal progressive necrotizing hepatocellular damage has been reported in a very few patients. Reversible jaundice.

Hematologic --Leukopenia.

Immunologic --Lupus-like syndrome.

Metabolic --Hypermetabolic syndrome (which may include, but is not limited to, hyperpyrexia,

tachycardia, tachypnea, muscular rigidity, elevated CK levels, metabolic acidosis, hypoxia, coma and may resemble an overdose).

Respiratory --Edema of the glottis.

General --Fever associated with increased muscle tone.

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 range from vivid nightmares with agitation to frank psychosis and convulsions. This syndrome generally responds to reinstitution of low–dose Nardil therapy followed by cautious downward titration and discontinuation.

DOSAGE AND ADMINISTRATION

Initial dose: The usual starting dose of Nardil 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 Nardil is achieved, dosage should be reduced slowly over several weeks. Maintenance dose may be as low as one tablet, 15 mg, a day or every other day, and should be continued for as long as is required.

OVERDOSAGE

Note --For management of *hypertensive crises* see WARNINGS section.

Accidental or intentional overdosage may be more common in patients who are depressed. It should be remembered that multiple drugs and/or alcohol may have been ingested.

Depending on the amount of overdosage with Nardil, 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 hospitalization, 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.

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 and, if necessary, blood pressure titration with an intravenous infusion of dilute pressor agent. 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 pathophysiologic effects of massive overdosage may persist for several days, since the drug acts by inhibiting physiologic enzyme systems. With symptomatic and supportive measures, recovery from *mild* overdosage may be expected within 3 to 4 days.

Hemodialysis, peritoneal dialysis, and charcoal hemoperfusion 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.

HOW SUPPLIED

Each Nardil tablet is orange, biconvex, glossy sugar–coated, and imprinted with "P–D 270" in brown ink and contains phenelzine sulfate equivalent to 15 mg of phenelzine base.

N 0071–0270–24 Bottles of 100

Storage: Store between 15°–30° C (59°–86°F).

Rx only
US Patent 3,314,855

Revised August 1998 **0270G081**

PRODUCT PHOTO(S):
NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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