CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

011909Orig1s030

Trade Name:	NARDIL
Generic or Proper Name:	(phenelzine sulfate)
Sponsor:	Parke Davis
Approval Date:	January 3, 2002
Indication:	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.

CENTER FOR DRUG EVALUATION AND RESEARCH

011909Orig1s030

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

011909Orig1s030

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-909/S-030

Pfizer Inc.
Attention: Denise Andrews
Regulatory Affairs
235 E 42nd Street
New York, NY 10017

Dear Ms. Andrews:

We acknowledge receipt of your supplemental new drug application dated October 17, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nardil (phenelzine sulfate) 15 mg Tablets.

This supplemental application provides for the addition of the Pfizer Inc. name to reflect that Pfizer Inc. has acquired the Warner-Lambert/Parke-Davis Company.

We have completed the review of this supplemental application, S-030, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 17, 2001/Label Code 0270G081Q), which incorporates all of the revisions listed above. Accordingly, this supplemental application is approved effective on the date of this letter.

Labeling changes of the kind which you have proposed are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplements, have been made.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

1/3/02 08:03:04 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

011909Orig1s030

LABELING

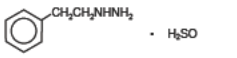
69-5995-00-3

NARDIL®

(Phenelzine Sulfate Tablets, USP)

DESCRIPTION

NARDIL® (phenelzine sulfate) is a potent inhibitor of monoamine oxidase (MAO). Phenelzine sulfate is a hydrazine derivative. It has a molecular weight of 234.27 and is chemically described as $C_8H_{12}N_2 \cdot H_2SO_4$. Its chemical structure is shown below:



Molecular weight 234.27

Each NARDIL film-coated tablet for oral administration contains phenelzine sulfate equivalent to 15 mg of phenelzine base and the following inactive ingredients: mannitol, USP; croscarmellose sodium, NF; povidone, USP; edetate disodium, USP; magnesium stearate, NF; isopropyl alcohol, USP; purified water, USP; opadry orange Y30-13242A; simethicone emulsion, USP.

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, citalopram, 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

CONTRAINDICATIONS *(continued)*

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
Antiappetite 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 that they are taking NARDIL.

WARNINGS *(continued)*

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
perphenazine and amitriptyline hydrochloride
clomipramine hydrochloride
desipramine hydrochloride
imipramine hydrochloride
doxepin
carbamazepine
cyclobenzaprine HCl
amoxapine
maprotiline HCl
trimipramine maleate
protriptyline HCl
mirtazapine

NARDIL should be used with caution in combination with antihypertensive drugs, including thiazide diuretics and β-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 (MAO) inhibitors in combination with serotoninergic agents (e.g., dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxine) there have been reports of serious, sometimes fatal, reactions. Because NARDIL is a monoamine oxidase (MAO) inhibitor, 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 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.

OVERDOSAGE *(continued)*

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, film-coated, and engraved with "P-D 270" and contains phenelzine sulfate equivalent to 15 mg of phenelzine base.

NDC 0071-0350-24. Bottles of 100

Storage:

Store between 15° - 30°C (59° - 86°F).

Rx only

Distributed by:

Pfizer

Parke-Davis

Division of Pfizer Inc, NY, NY 10017

8805232

69-5985-00-3

Revised May 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

011909Orig1s030

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA: 11-909

DRUG NAME: Nardil

INDICATION: Depression

SPONSOR: Pfizer

DATE OF SUBMISSION: 10/17/01

DATE RECEIVED: 10/18/01

MATERIAL RECEIVED: CBE-Labeling

I. REVIEW:

We have received a labeling change reflecting Pfizer acquiring Parke-Davis products. This change adds the Pfizer name in the appropriate places to the label.

II. RECOMMEDATION:

I recommend the labeling change be accepted as proposed.

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120

cc:file\tlaughren\ehearst\pdavid

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/s/

Earl Hearst
12/13/01 02:06:45 PM
MEDICAL OFFICER

Thomas Laughren
12/13/01 03:02:57 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

011909Orig1s030

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: December 14, 2001
NDA: 11-909
DRUG: Nardil (phenelzine sulfate) 15 mg Tablets
Sponsor: Pfizer
Supplements: SLR-030 (dated 10-17-01)

Notes of Interest:

- Last approved labeling supplement: SLR-029 (dated 8-14-98 and permitted on 3-28-00; Label Code 0270G081).

REVIEW

11-909/SLR-030
Dated: 10-17-01
CBE: Yes
Label Code: 0270G081Q
Reviewed by Medical Officer: Yes, acceptable

The supplement provides for the addition of the Pfizer Inc. name to reflect that Pfizer Inc. has acquired the Warner-Lambert/Parke-Davis Company.

CONCLUSIONS

1. The supplement only provides for the labeling revisions listed above.
2. The medical officer has reviewed the supplement, and has found the changes acceptable.
3. I recommend that an approval letter issue.

Paul David. R.Ph
Senior Regulatory Project Manager

Robbin Nighswander, R.Ph
Supervisory Regulatory Health Officer

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/s/

Paul David
12/20/01 10:43:19 AM
CSO

Robbin Nighswander
12/20/01 10:57:27 AM
CSO