CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-012/S-024 &
18-013/S-053

Trade Name:	Pamelor capsules, USP 10, 25, 50 and 75 mg Pamelor oral solution, USP 10mg/5mL
Generic Name:	nortriptyline HCl
Sponsor:	Tyco Healthcare
Approval Date:	7/31/2001
Indications:	For the relief of symptoms of depression.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-012/S-024 &

18-013/S-053

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-012/S-024 &

18-013/S-053

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-012/S-024
NDA 18-013/S-053

Novartis Pharmaceuticals
Attention: Mara Stiles
Associate Director, Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your supplemental new drug applications dated December 20, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pamelor (nortriptyline HCl) 10 mg/5 ml Solution (NDA 18-012) and Pamelor (nortriptyline HCl) 10 mg, 25 mg, 50 mg, and 75 mg Capsules (NDA 18-013)

We additionally refer to an Agency approvable letter dated February 13, 2001 for the above supplemental applications.

We acknowledge receipt of your submission dated June 8, 2001, providing for a response to our February 13, 2001, Agency letter.

These supplemental new drug applications provide for a new subsection under the **PRECAUTIONS** section entitled **Geriatric Use**.

Additionally, we note that you have also updated the storage condition statement of Pamelor Solution under the **HOW SUPPLIED** section.

We have completed the review of these supplemental applications 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 June 8, 2001/Label Code T2001-31/#89013201), which incorporates all of the revisions listed. Accordingly, these supplemental applications are approved effective on the date of this letter.

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
7/31/01 08:30:32 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-012/S-024 &

18-013/S-053

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-012/S-024
NDA 18-013/S-053

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your supplemental new drug applications dated December 20, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pamelor (nortriptyline HCl) Solution (NDA 18-012) and Pamelor (nortriptyline HCl) Capsules (NDA 18-013).

These "prior approval" supplemental new drug applications provide for a new subsection under the **PRECAUTIONS** section entitled **Geriatric Use** to comply with an August 27, 1997 Federal Register Notice requiring that sponsors of psychotropic drugs add geriatric use data to product labeling.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as stated below.

> **PRECAUTIONS-Geriatric Use**
> Clinical studies of Pamelor did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience indicates that, as with other tricyclic antidepressants, hepatic adverse events (characterized mainly by jaundice and elevated liver enzymes) are observed very rarely in geriatric patients and deaths associated with cholestatic liver damage have been reported in isolated instances. Cardiovascular function, particularly arrhythmias and fluctuations in blood pressure, should be monitored. There have also been reports of confusional states following tricyclic antidepressant administration in the elderly. Higher plasma concentrations of the active nortriptyline metabolite, 10-hydroxynortriptyline, have also been reported in elderly patients. As with other tricyclic antidepressants, dose selection for an elderly patient should usually be limited to the smallest effective total daily dose (see **DOSAGE AND ADMINISTRATION**).

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call 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

/s/

Russell Katz
2/13/01 11:00:08 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-012/S-024 &

18-013/S-053

LABELING

89013201

APPROVED

JUL 31 2001

T2001-31
89013201

NOVARTIS

Pamelor®

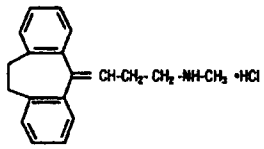
(nortriptyline HCl) capsules, USP
(nortriptyline HCl) oral solution, USP

Rx only

DESCRIPTION

Pamelor® (nortriptyline HCl) is 1-Propanamine, 3-(10,11-dihydro-5*H*-dibenzo[*a,d*] cyclohepten-5-ylidene)-*N*-methyl-, hydrochloride.

The structural formula is as follows:



$C_{19}H_{21}N$·HCl Mol. wt. 299.8

10 mg, 25 mg, 50 mg, and 75 mg Capsules

Active Ingredient: nortriptyline HCl, USP

10 mg, 25 mg, and 75 mg Capsules

Inactive Ingredients: D&C Yellow #10, FD&C Yellow #6, gelatin, silicone fluid, sodium lauryl sulfate, starch, and titanium dioxide.

May Also Include: benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

50 mg Capsules

Inactive Ingredients: gelatin, silicone fluid, sodium lauryl sulfate, starch, and titanium dioxide.

May Also Include: benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium bisulfite (capsule shell only), and sodium propionate.

Solution

Active Ingredient: nortriptyline HCl, USP

Inactive Ingredients: alcohol, benzoic acid, flavoring, purified water, and sorbitol.

ACTIONS

The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Pamelor® (nortriptyline HCl) is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that Pamelor® (nortriptyline HCl) interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that Pamelor® (nortriptyline HCl) has a combination of stimulant and depressant properties.

INDICATIONS

Pamelor® (nortriptyline HCl) is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

The use of Pamelor® (nortriptyline HCl) or other tricyclic antidepressants concurrently with a monoamine oxidase (MAO) inhibitor is contraindicated. Hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. It is advisable to have discontinued the MAO inhibitor for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. Patients hypersensitive to Pamelor® (nortriptyline HCl) should not be given the drug.

Cross-sensitivity between Pamelor® (nortriptyline HCl) and other dibenzazepines is a possibility.

Pamelor® (nortriptyline HCl) is contraindicated during the acute recovery period after myocardial infarction.

WARNINGS

Patients with cardiovascular disease should be given Pamelor® (nortriptyline HCl) only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, Pamelor® (nortriptyline HCl) should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when Pamelor® (nortriptyline HCl) is administered, inasmuch as this drug is known to lower the convulsive threshold. Great care is required if Pamelor® (nortriptyline HCl) is given to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Pamelor® (nortriptyline HCl) may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly.

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy

Safe use of Pamelor® (nortriptyline HCl) during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

Pediatric Use

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

PRECAUTIONS

The use of Pamelor® (nortriptyline HCl) in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If the drug is given to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, Pamelor® (nortriptyline HCl) may cause symptoms of the manic phase to emerge.

Troublesome patient hostility may be aroused by the use of Pamelor® (nortriptyline HCl). Epileptiform seizures may accompany its administration, as is true of other drugs of its class.

When it is essential, the drug may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery.

The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time.

Both elevation and lowering of blood sugar levels have been reported.

Drug Interactions

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

Close supervision and careful adjustment of the dosage are required when Pamelor® (nortriptyline HCl) is used with other anticholinergic drugs and sympathomimetic drugs.

Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. The patient should be informed that the response to alcohol may be exaggerated.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Drugs Metabolized by P450 2D6 – The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7%-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

Geriatric Use
Clinical studies of Pamelor® (nortriptyline HCl) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience indicates that, as with other tricyclic antidepressants, hepatic adverse events (characterized mainly by jaundice and elevated liver enzymes) are observed very rarely in geriatric patients and deaths associated with cholestatic liver damage have been reported in isolated instances. Cardiovascular function, particularly arrhythmias and fluctuations in blood pressure, should be monitored. There have also been reports of confusional states following tricyclic antidepressant administration in the elderly. Higher plasma concentrations of the active nortriptyline metabolite, 10-hydroxynortriptyline, have also been reported in elderly patients. As with other tricyclic antidepressants, dose selection for an elderly patient should usually be limited to the smallest effective total daily dose (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
Note: Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

Cardiovascular – Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric – Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurologic – Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus.

Anticholinergic – Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic – Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.

Hematologic – Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal – Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, blacktongue.

Endocrine – Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other – Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms – Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION
Pamelor® (nortriptyline HCl) is not recommended for children.

Pamelor® (nortriptyline HCl) is administered orally in the form of capsules or liquid. Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalized patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Usual Adult Dose – 25 mg three or four times daily; dosage should begin at a low level and be increased as required. As an alternate regimen, the total daily dosage may be given once a day. When doses above 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50-150 ng/mL. Doses above 150 mg/day are not recommended.

Elderly and Adolescent Patients – 30-50 mg/day, in divided doses, or the total daily dosage may be given once a day.

OVERDOSAGE
Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

Manifestations:
Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, shock, congestive heart failure, pulmonary edema, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, restlessness, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the acute symptoms listed under ADVERSE REACTIONS. There have been reports of patients recovering from nortriptyline overdoses of up to 525 mg.

Management:
General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. EMESIS IS CONTRAINDICATED.

Cardiovascular: A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a pCO_2 <20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED
Pamelor® (nortriptyline HCl) Capsules, USP
Pamelor® (nortriptyline HCl) Capsules, USP, equivalent to 10 mg, 25 mg, 50 mg, and 75 mg base, are available in bottles of 100 (10 mg: NDC 0078-0086-05; 25 mg: NDC 0078-0087-05; 50 mg: NDC 0078-0078-05; 75 mg: NDC 0078-0079-05). 10 mg, 25 mg, and 50 mg are available in a unit dose package of 100 individually labeled blisters, each containing 1 capsule (10 mg: NDC 0078-0086-06; 25 mg: NDC 0078-0087-06; 50 mg: NDC 0078-0078-06). Pamelor® (nortriptyline HCl) Capsules, USP 25 mg is also available in bottles of 500 (NDC 0078-0087-08).

10 mg capsules branded " SANDOZ" on one half, " PAMELOR 10 mg" other half; 25 mg capsules branded " SANDOZ" on one half, " PAMELOR 25 mg" other half; 50 mg capsules branded " SANDOZ" on one half, " PAMELOR 50 mg" other half; and 75 mg capsules branded " SANDOZ" on one half, " PAMELOR 75 mg" other half.

Store and Dispense
Below 86°F (30°C); tight container.

Pamelor® (nortriptyline HCl) Solution, USP
Pamelor® (nortriptyline HCl) Solution, USP, equivalent to 10 mg base per 5 mL, is supplied in 16-fluid-ounce bottles (NDC 0078-0016-33). Alcohol content 4%.

Store and Dispense
Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) tight, light-resistant container. [See USP Controlled Room Temperature]

Solution Manufactured by:
Novartis Consumer Health, Inc.
Lincoln, Nebraska 68517

Capsules Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

REV: APRIL 2001 Printed in U.S.A. T2001-31
89013201

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-012/S-024 &

18-013/S-053

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	18-012
DRUG:	Pamelor® Solution {nortriptyline HCl}
SPONSOR:	Novartis
CORRESPONDENCE DATE:	December 20, 2000
DATE RECEIVED:	December 27, 2000

The sponsor has submitted a supplement for approval providing a proposed revision to the labeling to include a geriatric use subsection under precautions. They completed a review of available controlled studies, of information gathered from other studies and post marketing experience, and of pertinent information from well-documented studies discovered via a literature search.

The proposed text of the new geriatric use subsection under Precautions is as follows:

Geriatric Use: Clinical studies of Pamelor did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently form younger subjects. Other reported clinical experience indicates that, as with other tricyclic antidepressants, hepatic adverse events (characterized mainly by jaundice and elevated liver enzymes) are observed very rarely in geriatric patients and deaths associated with cholestatic liver damage have been reported in isolated instances. Cardiovascular function, particularly arrhythmias and fluctuation in blood pressure, should be monitored. [redacted] b(4) [redacted]

II. RECOMMEDATION:

This labeling, although adequate, is different from the geriatric section for Aventyl, which I have attached to this review. I would not object to this labeling but it might be preferable to suggest the same labeling already approved for Aventyl.

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120
cc:file\tlaughren\ehearst\pdavid

/s/

Earl Hearst
1/8/01 09:08:26 AM
MEDICAL OFFICER

Thomas Laughren
1/12/01 07:52:40 PM
MEDICAL OFFICER
I agree that the sections should be the same; we might suggest combini
ng the best features of both.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	18-013
DRUG:	Pamelor® Capsules {nortriptyline HCl}
SPONSOR:	Novartis
CORRESPONDENCE DATE:	December 20, 2000
DATE RECEIVED:	December 27, 2000

The sponsor has submitted a supplement for approval providing a proposed revision to the labeling to include a geriatric use subsection under precautions. They completed a review of available controlled studies, of information gathered from other studies and post marketing experience, and of pertinent information from well-documented studies discovered via a literature search.

The proposed text of the new geriatric use subsection under Precautions is as follows:

Geriatric Use: Clinical studies of Pamelor did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently form younger subjects. Other reported clinical experience indicates that, as with other tricyclic antidepressants, hepatic adverse events (characterized mainly by jaundice and elevated liver enzymes) are observed very rarely in geriatric patients and deaths associated with cholestatic liver damage have been reported in isolated instances. Cardiovascular function, particularly arrhythmias and fluctuation in blood pressure, should be monitored. [redacted] b(4) [redacted]

II. RECOMMEDATION:

This labeling, although adequate, is different from the geriatric section for Aventyl, which I have attached to this review. I would not object to this labeling but it might be preferable to suggest the same labeling already approved for Aventyl.

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120
cc:file\tlaughren\ehearst\pdavid

/s/

Earl Hearst
1/8/01 09:19:54 AM
MEDICAL OFFICER

Thomas Laughren
1/12/01 07:50:18 PM
MEDICAL OFFICER
I agree that the sections should be the same; we might suggest combini
ng the best features of both.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-012/S-024 &

18-013/S-053

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date of Review:	July 20, 2001
Drug:	Pamelor (nortriptyline HCl) 10 mg/5 ml Solution (NDA 18-012) and Pamelor (nortriptyline HCl) 10 mg, 25 mg, 50 mg, and 75 mg Capsules (NDA 18-013)
Sponsor:	Novartis Pharmaceuticals
Supplement:	NDA 18-012/S-024 dated 12-20-00 and amended on 6-8-01 NDA 18-013/S-053 dated 12-20-00 and amended on 6-8-01

Note of interest:

- The last approved labeling supplements, 18-012/SLR-022 and 18-013/S-049, were approved in an Agency letter dated 7-8-96.
- The Agency issued an approvable letter for NDAs 18-012/S-024 and 18-013/S-053 in a letter dated 2-13-01.

REVIEW

NDA 18-012/S-024
NDA 18-013/S-053
Dated: 12-20-00 and amended on 6-8-01
Label Code: T2001-31 (#89013201)
CBE: No, Prior Approval
Reviewed by Medical Officer: Yes, acceptable

These supplemental applications provide for a new subsection under the **PRECAUTIONS** section entitled **Geriatric Use**.

- The sponsor responded to the Agency approvable letter dated 2-13-01, with changes to the labeling, verbatim, as requested in the Agency letter.

- The sponsor has also taken the opportunity to update their storage condition statement of Pamelor Solution at the end of the **HOW SUPPLED** section.

- Although not stated in the cover letter, the supplement revises the title of the subsection entitled **Use in Children** to **Pediatric Use**.

CONCLUSIONS

1. The labeling only provides for the changes as listed in the Agency AE letter dated 2-13-01 except for the two notations above when compared to the last approved labeling for Pamelor, 18-012/SLR-022 and 18-013/S-049.

2. I recommend that the chemist make a cursory review of the updated storage condition statement of Pamelor Solution for acceptability.

3. If the storage statement is acceptable, I recommend that an approval letter issue for these supplemental applications.

Paul David. RPh
Regulatory Project Manager

Robbin Nighswander
Supervisory Consumer Safety Officer

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

/s/

Paul David
7/24/01 08:16:53 AM
CSO

Robbin Nighswander
7/24/01 01:50:55 PM
CSO