CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19787/S013

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA ~~19~~-684/012
19-787/013

JAN 8 1997

Pfizer Inc.
Attention: Ms. Rita Wittich
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Wittich:

We acknowledge receipt on November 19, 1996 of your November 18, 1996 supplemental new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procardia XL (nifedipine) Tablets (NDA 19-684) and Norvasc (amlodipine besylate) Tablets (NDA 19-787).

The supplemental applications provide for final printed labeling revised under **ADVERSE REACTIONS** to include gynecomastia as an adverse event associated with the use of the drugs.

We have completed the review of these supplemental applications and they are approved effective on the date of this letter.

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

Should you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
Telephone: (301) 594-5313

Sincerely yours,

/S/ 1/7/97

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S013

FINAL PRINTED LABELING

NDA No: 19-781 Rec'd. 11-14-96

Reviewed by: Rudick 1-7-97

APPROVED

JAN 8 1997

69-4782-00-5

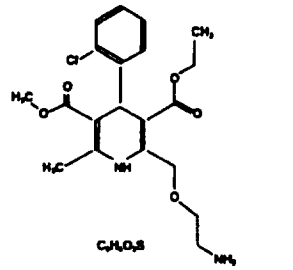
Norvasc®

(amlodipine besylate) Tablets

DESCRIPTION

NORVASC® is the besylate salt of amlodipine, a long-acting calcium channel blocker.

NORVASC is chemically described as (R,S) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl) -4 - (2-chlorophenyl) - 1,4 - dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula is:



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. NORVASC (amlodipine besylate) tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: NORVASC is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that NORVASC binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. NORVASC inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by NORVASC. Within the physiologic pH range, NORVASC is an ionized compound (p*K*a=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

NORVASC is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which NORVASC relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, NORVASC reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: NORVASC has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of NORVASC in vasospastic (Prinzmetal's or variant) angina.

Pharmacokinetics and Metabolism: After oral administration of therapeutic doses of NORVASC, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of NORVASC is not altered by the presence of food.

NORVASC is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of NORVASC are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of NORVASC are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Pharmacodynamics: *Hemodynamics* Following administration of therapeutic doses to patients with hypertension, NORVASC produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with NORVASC is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/−2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of NORVASC resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with NORVASC have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, NORVASC has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Studies in Patients with Congestive Heart Failure: NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of NORVASC 5-10 mg in 1153 patients with NYHA classes III (n=831) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, NORVASC had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on NORVASC and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Electrophysiologic Effects: NORVASC does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving NORVASC and concomitant beta blockers. In clinical studies in which NORVASC was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, NORVASC therapy did not alter electrocardiographic intervals or produce higher degrees of AV block.

Effects in Hypertension: The antihypertensive efficacy of NORVASC has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on NORVASC and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Effects in Chronic Stable Angina: The effectiveness of 5-10 mg/day of NORVASC in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 NORVASC, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for NORVASC 10 mg, and averaged 7.9% (38 sec) for NORVASC 5 mg. NORVASC 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of NORVASC in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Effects in Vasospastic Angina: In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, NORVASC therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 NORVASC and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

INDICATIONS AND USAGE

1. Hypertension

NORVASC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2. Chronic Stable Angina

NORVASC is indicated for the treatment of chronic stable angina. NORVASC may be used alone or in combination with other antianginal agents.

3. Vasospastic Angina (Prinzmetal's or Variant Angina)

NORVASC is indicated for the treatment of confirmed or suspected vasospastic angina. NORVASC may be used as monotherapy or in combination with other antianginal drugs.

CONTRAINDICATIONS

NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS

General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker

[redacted]

PRECAUTIONS *(continued)*

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (1 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m² basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

*Based on patient weight of 50 kg.

ADVERSE REACTIONS

NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies

	NORVASC (%) (N=1730)	PLACEBO (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.8

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

ADR	NORVASC M=% (N=1218)	NORVASC F=% (N=512)	PLACEBO M=% (N=914)	PLACEBO F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.8	0.8	0.3

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension.

Central and Peripheral Nervous System: hypoesthesia, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting, gingival hyperplasia.

General: asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,** myalgia.

Psychiatric: sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,** epistaxis.

Skin and Appendages: pruritus,** rash,** rash erythematous, rash maculopapular.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: thirst.

Hemopoietic: purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, paroxmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE

Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

The usual initial antihypertensive oral dose of NORVASC is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding NORVASC to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS section for information related to dosage and side effects.

Co-administration with Other Antihypertensive and/or Antianginal Drugs: NORVASC has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

HOW SUPPLIED

NORVASC®—2.5 mg Tablets (amlodipine besylate equivalent to 2.5 mg of amlodipine per tablet) are supplied as white, diamond, flat-faced, beveled edged engraved with "NORVASC" on one side and "2.5" on the other side and supplied as follows:

NDC 0069-1520-66	Bottle of 100

NORVASC®—5 mg Tablets (amlodipine besylate equivalent to 5 mg of amlodipine per tablet) are white, elongated octagon, flat-faced, beveled edged engraved with both "NORVASC" and "5" on one side and plain on the other side and supplied as follows:

NDC 0069-1530-66	Bottle of 100
NDC 0069-1530-41	Unit Dose package of 100
NDC 0069-1530-72	Bottle of 300

NORVASC®—10 mg Tablets (amlodipine besylate equivalent to 10 mg of amlodipine per tablet) are white, round, flat-faced, beveled edged engraved with both "NORVASC" and "10" on one side and plain on the other side and supplied as follows:

NDC 0069-1540-66	Bottle of 100
NDC 0069-1540-41	Unit Dose package of 100

Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP).

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

Printed in U.S.A.
69-4782-00-5 Revised October 1996

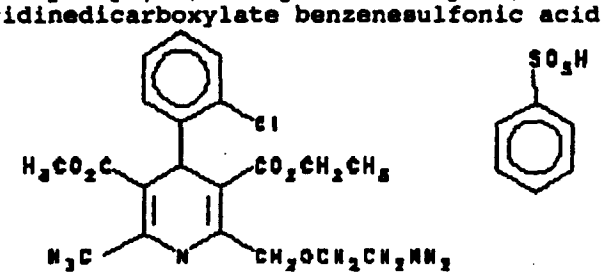
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S013

CHEMISTRY REVIEW(S)

NOV 26 1996

37.1

CHEMIST'S REVIEW	1. ORGANIZATION HFD - 110	2. NDA Number 19-787
3. Name and Address of Applicant (City & State) Pfizer, Inc. Eastern Point Road Groton, CT 06340		4. Supplement(s) Number(s) SLR-013 Date(s) 11-18-96
5. Drug Name NORVASC	6. Nonproprietary Name Amlodipine Besylate	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Final Printed Labeling as per Agency's request.		
9. Pharmacological Category Antihypertensive and Antianginal	10. How Dispensed /X/ RX /__/ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet	13. Potency(ies) 2.5, 5, and 10 mg	
14. Chemical Name and Structure 3-Ethyl-5-methyl-2-(2-aminoethoxymethl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonic acid 		15. Records/Reports Current /X/ Yes /__/ No Reviewed /X/ Yes /__/ No

16. Comments:

As per Agency's letter of September 24, 1996 regarding the overdosage section the labelling was modified to strengthen the Overdosage section.

17. Conclusions and Recommendations:

The labeling did not effect CMC related sections.

18. REVIEWER

Name	Signature	Date Completed
Ramsharan D. Mittal	/S/	11/26/96

19. Distribution:
/__/ Original Jacket /__/ Reviewer /__/ Division File /__/ CSO

/S/

11/26/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S013

ADMINISTRATIVE DOCUMENTS

RHPM Review of Final Printed Labeling

Application: NDA 19-684/S-012
Procardia XL (nifedipine) Tablets

NDA 19-787/S-013
Norvasc (amlodipine besylate) Tablets

Sponsor: Pfizer Inc.

Supplement Date: November 18, 1996

Receipt Date: November 19, 1996

Type of Supplement: **Special Supplement: Changes Being Effected**

Review

We issued a letter to the sponsor on September 26, 1996 asking them to add gynecomastia to the list of adverse events associated with the use of nifedipine and amlodipine. The sponsor submitted final printed labeling as a "Special Supplement: Changes Being Effected" in which gynecomastia was added to the **ADVERSE REACTIONS** section of the package insert of each product as a post-marketing event for which causality is not certain.

No other changes were made to either package insert.

Recommendation

I recommend that these supplemental applications be approved.

/S/

David Roeder
Regulatory Health Project Manager

dr/11-26-96

cc: NDA 19-684
NDA 19-787
HFD-110
HFD-111/DRoeder/SBenton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S013

CORRESPONDENCE

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 2503 Fax 212 573 15

Pfizer

ORIGINAL

Inna Kissen, PhD
Associate Director

November 18, 1996

NDA NO. 19-787 REF. NO. 013
NDA SUPPL FOR SLR

Raymond Lipicky, M.D., Director
Division of Cardio-Renal
Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: Procardia XL (nifedipine) Extended Release Tablets
NDA #19-684
Procardia (nifedipine) Capsules
NDA #18-482*
NORVASC (Amlodipine besylate) tablets
NDA #19-787
Supplemental Application - Changes Being Effected

Dear Dr. Lipicky;

Please refer to your letter dated September 24, 1996 regarding the Overdosage section for the above products and an addition of gynecomastia to the Adverse Reaction section.

In the letter you suggested that based on the paper entitled: "Calcium Channel Blocking Drug Overdose: an Australian Series" the following language should be added to strengthen the Overdosage section:

The calcium channel blockers are a heterogeneous class of agents. We feel that this addition is inappropriate for Norvasc, Procardia XL, Procardia Capsules, and for dihydropyridines (DHPs) in general for the following reasons:

1) Bradycardia may occur following administration and particularly overdose of phenylalkylamines (verapamil) and benzothiazipines (diltiazem). DHPs elicit either no change in heart rate or an increase in heart rate. For the cases listed in the Australian paper, heart rates following overdosage with nifedipine were either high or on the high side of normal.

2) The proposed labeling is suggestive that atropine would be an appropriate treatment for an overdose with a calcium channel blocker. As a cholinergic blocker, atropine would be expected to increase heart rate. While this may be beneficial following an overdose of verapamil or diltiazem, increasing heart rate would not be a goal following an overdose with a DHP where heart rates may already be elevated.

3) The Australian paper that is the basis of the proposed labeling addition does not support the use of intravenous calcium chloride or calcium gluconate following an overdose of a DHP.

a) The paper states:

"High dose intravenous calcium is required to reverse CCB cardiotoxicity. The dose required is that needed to reverse arrhythmias. Junctional bradycardia with transient complete heart block was the most frequently observed arrhythmia. This was noted to be correctable with adequate intravenous calcium chloride and/or calcium gluconate."

Arrhythmias are not normally associated with DHPs. For the DHP(nifedipine) cases listed in the above paper (Table 1), there were no ECG changes following the nifedipine monotherapy overdosage. Even with the massive overdose of 4800 mg of Procardia XL taken my a patient attempting suicide, no ECG abnormalities were noted (see Procardia XL Package Insert, the Overdosage section).

b) Table 1 of the Australian paper indicates that neither of the nifedipine overdose patients were given an intravenous infusion containing calcium. Therefore, this paper provides no data supporting the intravenous infusion of calcium chloride or calcium gluconate following an overdose with a DHP.

The current Ovedosage wording for Norvasc, Procardia XL, and Procardia Capsules is clinically appropriate.

In addition, your letter requested that gynecomastia should be added to Norvasc, Procardia XL and Procardia Capsules package inserts. The following wording is added to the Adverse Reaction section of Norvasc package insert:

The following postmarketing event has been reported infrequently where a casual relationship is uncertain: gynecomastia.

"Gynecomastia" is also added to the marketing experience paragraph of the Procardia XL Adverse Reaction section. Procardia Capsules package insert does not require revisions since it contains gynecomastia in the Adverse Reaction section.

We are submitting sixteen copies of the final printed labeling for Procardia XL (nifedipine) Extended Release Tablets and Norvasc (amlodipine besylate) Tablets, ten of which are individually mounted. The highlighted copies of the package inserts are also enclosed. The above changes will be placed into the effect as of the mid December 1996.

If you have any questions, please contact my office at (212) 573-2503.

Sincerely,

I. Kissen

Inna Kissen, Ph.D.

Enclosure
IK:amw
NORV2/6

* Cover letter only

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CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
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