CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-998/S017

Trade Name: Vasotec

Generic Name: Enalpril Maleate

Sponsor: Merck Research Laboratories

Approval Date: February 16, 1991

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S017

APPROVAL LETTER

FEB 20 1991

NDA 18-998/S-017

Merck Sharp & Dohme Research Laboratories
Attention: Elliott Berger
West Point, PA 19486

Dear Dr. Berger:

Please refer to your January 31, 1989 supplemental new drug application resubmitted on July 24, 1990 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate, MSD) Tablets.

We also acknowledge receipt of your amendments dated October 23, December 19, 1990 and February 11, 1991.

The supplemental application provides for an alternate site for the manufacture and control of the dosage form by Merck Sharp & Dohme's corporate entity: Merck Sharp & Dohme Quimica de Puerto Rico, Inc., Caguas, Puerto Rico 00626 at a dedicated site leased from MOVA Pharmaceutical Corporation, Caguas, Puerto Rico.

We have completed the review of this supplemental application and it is approved.

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

Sincerely yours,

RW 2-20-91

Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
BUF-DO
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-100
HFD-232 (with labeling)
HFD-730
HFD-110/SZimmerman/2/14/91;2/15/91
clb/2/15/91;2/19/91/N18998.ltr
R/D init: RWolters/2/19/91

Stuart Zimmerman 2/19/91

Approval Date: 12/24/85

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S017

APPROVABLE LETTER

JAN 29 1991

NDA 18-998/S-017

Merck Sharp & Dohme Research Laboratories
Attention: Elliott T. Berger
Sumneytown Pike
West Point, PA 19486

Dear Dr. Berger:

Please refer to your January 31, 1989 supplemental new drug application resubmitted on July 24, 1990 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate, MSD) Tablets.

We also acknowledge receipt of your amendments dated October 23 and December 19, 1990.

The supplemental application provides for an alternate site for the manufacture and control of the dosage form by Merck Sharp & Dohme, Caguas, Division of Merck Sharp & Dohme, Quimica de Puerto Rico, Inc., Caguas, Puerto Rico (MPHD Caguas) at a dedicated site leased from MOVA Pharmaceutical Corporation, Caguas, Puerto Rico.

We have completed the review of this supplemental application. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed container labels, seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the supplemental application.

cc:
NWK-DO
Orig. NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/SZimmerman/12/21/90
clb/12/21/90;12/26/90/3392C

APPROVABLE

Sincerely yours,

1/29/91

Robert J. Wolters, Ph.D.
Supervisory Chemist
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:

18-998/S017

LABELING

Labeling: Unannotated 1
NDA No: NDA 18-998 Rec'd. 2-7-91
Reviewed by: K Bergman
2-14-91

A.H.F.S. Categories: 24:04, 24:08

APPROVED FEB 20 1991

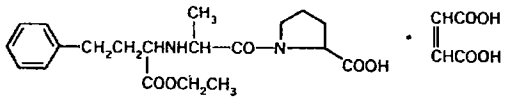
TABLETS

MSD | VASOTEC® (ENALAPRIL MALEATE, MSD)

VASOTEC®
(Enalapril Maleate, MSD)

DESCRIPTION

VASOTEC® (Enalapril Maleate, MSD) is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and its structural formula is:



Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Enalapril maleate is supplied as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets for oral administration. In addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients: lactose, magnesium stearate, starch, and other ingredients. The 2.5 mg, 10 mg and 20 mg tablets also contain iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with VASOTEC alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with VASOTEC plus a thiazide diuretic, there was essentially no change in serum potassium. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of VASOTEC remains to be elucidated.

While the mechanism through which VASOTEC lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, VASOTEC is antihypertensive even in patients with low-renin hypertension. Although VASOTEC was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

Pharmacokinetics and Metabolism

Following oral administration of VASOTEC, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of VASOTEC is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40 percent of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With glomerular filtration rate ≤30 mL/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. (See DOSAGE AND ADMINISTRATION.) Enalaprilat is dialyzable at the rate of 62 mL/min.

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VASOTEC®
(Enalapril Maleate, MSD)

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

Pharmacodynamics and Clinical Effects

Hypertension: Administration of VASOTEC to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients. (See WARNINGS.)

In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours.

At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval (see DOSAGE AND ADMINISTRATION).

In some patients achievement of optimal blood pressure reduction may require several weeks of therapy.

The antihypertensive effects of VASOTEC have continued during long term therapy. Abrupt withdrawal of VASOTEC has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of VASOTEC, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

When given together with thiazide-type diuretics, the blood pressure lowering effects of VASOTEC are approximately additive.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving VASOTEC. In this study there was no evidence of a blunting of the antihypertensive action of VASOTEC.

Heart Failure: In trials in patients treated with digitalis and diuretics, treatment with enalapril resulted in decreased systemic vascular resistance, blood pressure, pulmonary capillary wedge pressure and heart size, and increased cardiac output and exercise tolerance. Heart rate was unchanged or slightly reduced, and mean ejection fraction was unchanged or increased. There was a beneficial effect on severity of heart failure as measured by the New York Heart Association (NYHA) classification and on symptoms of dyspnea and fatigue. Hemodynamic effects were observed after the first dose, and appeared to be maintained in uncontrolled studies lasting as long as four months. Effects on exercise tolerance, heart size, and severity and symptoms of heart failure were observed in placebo-controlled studies lasting from eight weeks to over one year.

A Scandinavian multicenter trial compared the effects of enalapril and placebo on mortality in 253 patients with severe heart failure (NYHA Class IV) and radiographic evidence of cardiomegaly who were maintained on therapy with diuretics and digitalis. Other vasodilators were used as needed. In the enalapril group, the reduction in all-cause mortality was 40 percent after six months and 31 percent after one year. There was an improvement in NYHA classification, a reduction in heart size, and a lessened need for concomitant vasodilator therapy in the enalapril group.

INDICATIONS AND USAGE

Hypertension

VASOTEC is indicated for the treatment of hypertension.

VASOTEC is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of VASOTEC and thiazides are approximately additive.

Heart Failure

VASOTEC is indicated as adjunctive therapy in the management of heart failure, in patients who are not responding adequately to diuretics and digitalis.

In patients with severe heart failure, VASOTEC improves survival. In a multicenter placebo-controlled trial in patients with severe heart failure (New York Heart Association Class IV) and radiographic evidence of cardiomegaly who were maintained on therapy with diuretics and digitalis, patients who received VASOTEC had improved survival compared to placebo. (See CLINICAL PHARMACOLOGY.)

	SURVIVAL (%)	
	Six Months	One Year
VASOTEC (n = 127)	74	64
Placebo (n = 126)	56	48

VASOTEC is to be used with diuretics and digitalis.

In using VASOTEC consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that VASOTEC does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS

VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

VASOTEC®
(Enalapril Maleate, MSD)

WARNINGS

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including VASOTEC. In such cases VASOTEC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Hypotension

Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors, including VASOTEC, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Enalapril crosses the human placenta. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the fetus; limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Patients who do require ACE inhibitors during the second and third trimesters of pregnancy should be apprised of the potential hazards to the fetus, and frequent ultrasound examinations should be performed to look for oligohydramnios. If oligohydramnios is observed, VASOTEC should be discontinued unless it is considered life-saving for the mother.

Other potential risks to the fetus/neonate exposed to ACE inhibitors include: intrauterine growth retardation, prematurity, patent ductus arteriosus; fetal death has also been reported. It is not clear, however, whether these reported events are related to ACE inhibition or the underlying maternal disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion.

Enalapril has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day but not at 30 mg/kg/day (50 times the maximum human dose).

If VASOTEC is used during pregnancy or if the patient becomes pregnant while taking VASOTEC, the patient should be apprised of the potential hazards to the fetus.

VASOTEC®
(Enalapril Maleate, MSD)

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8 percent of patients but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions*.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Pregnancy

Pregnancy Category D. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers

Enalapril and enalaprilat are detected in human milk in trace amounts. Caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

For the most part, adverse experiences were mild and transient in nature. In clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 3.3 percent of patients with hypertension and in 5.7 percent of patients with heart failure. The frequency of adverse experiences was not related to total daily dosage within the usual dosage ranges. In patients with hypertension the overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

HYPERTENSION

Adverse experiences occurring in greater than one percent of patients with hypertension treated with VASOTEC in controlled clinical trials are shown below. In patients treated with VASOTEC, the maximum duration of therapy was three years; in placebo treated patients the maximum duration of therapy was 12 weeks.

	VASOTEC (n=2314) Incidence (discontinuation)	Placebo (n=230) Incidence
Body As A Whole		
Fatigue	3.0 (<0.1)	2.6
Orthostatic Effects	1.2 (<0.1)	0.0
Asthenia	1.1 (0.1)	0.9
Digestive		
Diarrhea	1.4 (<0.1)	1.7
Nausea	1.4 (0.2)	1.7
Nervous/Psychiatric		
Headache	5.2 (0.3)	9.1
Dizziness	4.3 (0.4)	4.3
Respiratory		
Cough	1.3 (0.1)	0.9
Skin		
Rash	1.4 (0.4)	0.4

HEART FAILURE

Adverse experiences occurring in greater than one percent of patients with heart failure treated with VASOTEC are shown below. The incidences represent the experiences from both controlled and uncontrolled clinical trials (maximum duration of therapy was approximately one year). In the placebo treated patients, the incidences reported are from the controlled trials (maximum duration of therapy is 12 weeks). The percentage of patients with severe heart failure (NYHA Class IV) was 29 percent and 43 percent for patients treated with VASOTEC and placebo, respectively.

	VASOTEC (n=673) Incidence (discontinuation)	Placebo (n=339) Incidence
Body As A Whole		
Orthostatic Effects	2.2 (0.1)	0.3
Syncope	2.2 (0.1)	0.9
Chest Pain	2.1 (0.0)	2.1
Fatigue	1.8 (0.0)	1.8
Abdominal Pain	1.6 (0.4)	2.1
Asthenia	1.6 (0.1)	0.3
Cardiovascular		
Hypotension	6.7 (1.9)	0.6
Orthostatic Hypotension	1.6 (0.1)	0.3
Angina Pectoris	1.5 (0.1)	1.8
Myocardial Infarction	1.2 (0.3)	1.8
Digestive		
Diarrhea	2.1 (0.1)	1.2
Nausea	1.3 (0.1)	0.6
Vomiting	1.3 (0.0)	0.9

*Based on patient weight of 50 kg

VASOTEC®
(Enalapril Maleate, MSD)

	VASOTEC (n=673) Incidence (discontinuation)	Placebo (n=339) Incidence
Nervous/Psychiatric		
Dizziness	7.9 (0.6)	0.6
Headache	1.8 (0.1)	0.9
Vertigo	1.6 (0.1)	1.2
Respiratory		
Cough	2.2 (0.0)	0.6
Bronchitis	1.3 (0.0)	0.9
Dyspnea	1.3 (0.1)	0.4
Pneumonia	1.0 (0.0)	2.4
Skin		
Rash	1.3 (0.0)	2.4
Urogenital		
Urinary Tract Infection	1.3 (0.0)	2.4

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5 to 1.0 percent of patients with hypertension or heart failure in clinical trials are listed below and, within each category, are in order of decreasing severity.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis (hepatocellular (proven on rechallenge) or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), impotence.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9 percent and syncope occurred in 0.5 percent of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. In heart failure patients, hypotension occurred in 6.7 percent and syncope occurred in 2.2 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9 percent of patients with heart failure. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: In infants exposed *in utero* to ACE inhibitors the following adverse experiences have been reported: Fetal and neonatal death, renal failure, hypoplastic lung development, hypotension, hyperkalemia, skull hypoplasia, limb contractures, craniofacial deformities, intrauterine growth retardation, prematurity and patent ductus arteriosus (see WARNINGS, *Fetal/Neonatal Morbidity and Mortality*).

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2 percent of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11 percent of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2 percent of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in either hypertension or congestive heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

7576624

OVERDOSAGE

Limited data are available in regard to overdosage in humans.

The oral LD_{50} of enalapril is 2000 mg/kg in mice and rats.

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Hypertension

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment

The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Normal Renal Function	>80 mL/min	5 mg
Mild Impairment	≤80 >30 mL/min	5 mg
Moderate to Severe Impairment	≤30 mL/min	2.5 mg
Dialysis Patients	—	2.5 mg on dialysis days*

*Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Heart Failure

VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) If possible, the dose of the diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice daily dosing. In addition, patients in the mortality trial received therapy twice daily (see below). Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

In a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 - 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*.)

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia

In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS and PRECAUTIONS, *Drug Interactions*.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

HOW SUPPLIED

No. 3411 — Tablets VASOTEC, 2.5 mg, are yellow, biconvex barrel shaped, scored, compressed tablets with code MSD 014 on one side and VASOTEC on the other. They are supplied as follows:
NDC 0006-0014-68 bottles of 100 (with desiccant)
NDC 0006-0014-28 unit dose packages of 100.

No. 3412 — Tablets VASOTEC, 5 mg, are white, barrel shaped, scored, compressed tablets, with code MSD 712 on one side and VASOTEC on the other. They are supplied as follows:
NDC 0006-0712-68 bottles of 100 (with desiccant)
(6505-01-236-8880, 5 mg 100's)
NDC 0006-0712-28 unit dose packages of 100.

No. 3413 — Tablets VASOTEC, 10 mg, are salmon, barrel shaped, compressed tablets, with code MSD 713 on one side and VASOTEC on the other. They are supplied as follows:
NDC 0006-0713-68 bottles of 100 (with desiccant)
(6505-01-236-8881, 10 mg 100's)
NDC 0006-0713-28 unit dose packages of 100.

No. 3414 — Tablets VASOTEC, 20 mg, are peach, barrel shaped, compressed tablets, with code MSD 714 on one side and VASOTEC on the other. They are supplied as follows:
NDC 0006-0714-68 bottles of 100 (with desiccant)
(6505-01-237-0545, 20 mg 100's)
NDC 0006-0714-28 unit dose packages of 100.

Storage

Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture.

Dispense in a tight container, if product package is subdivided.

Distributed by:

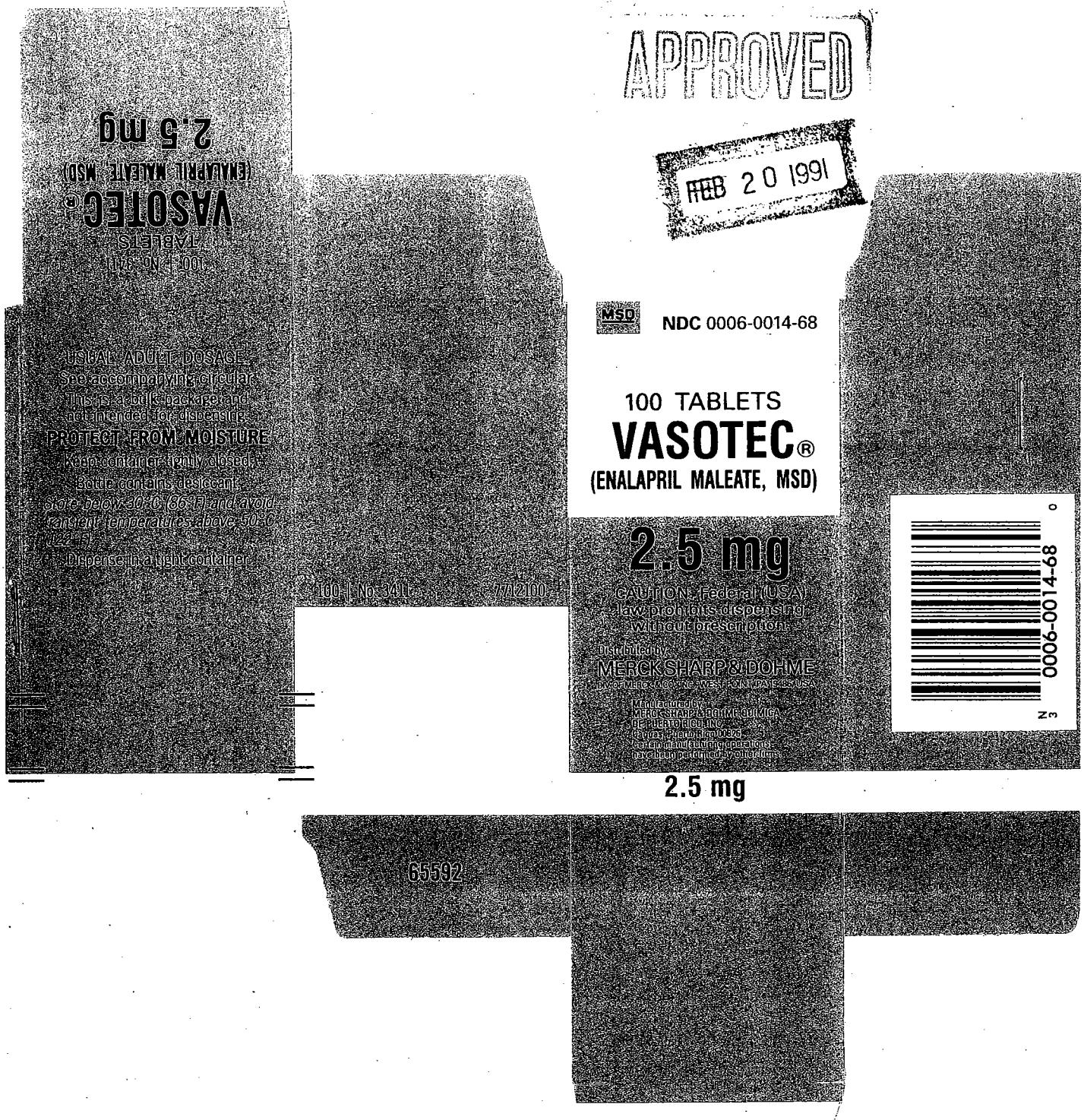
MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA

Manufactured by:

MERCK SHARP & DOHME QUIMICA
DE PUERTO RICO, Inc.
Caguas, Puerto Rico 00626
Certain manufacturing operations
have been performed by other firms.

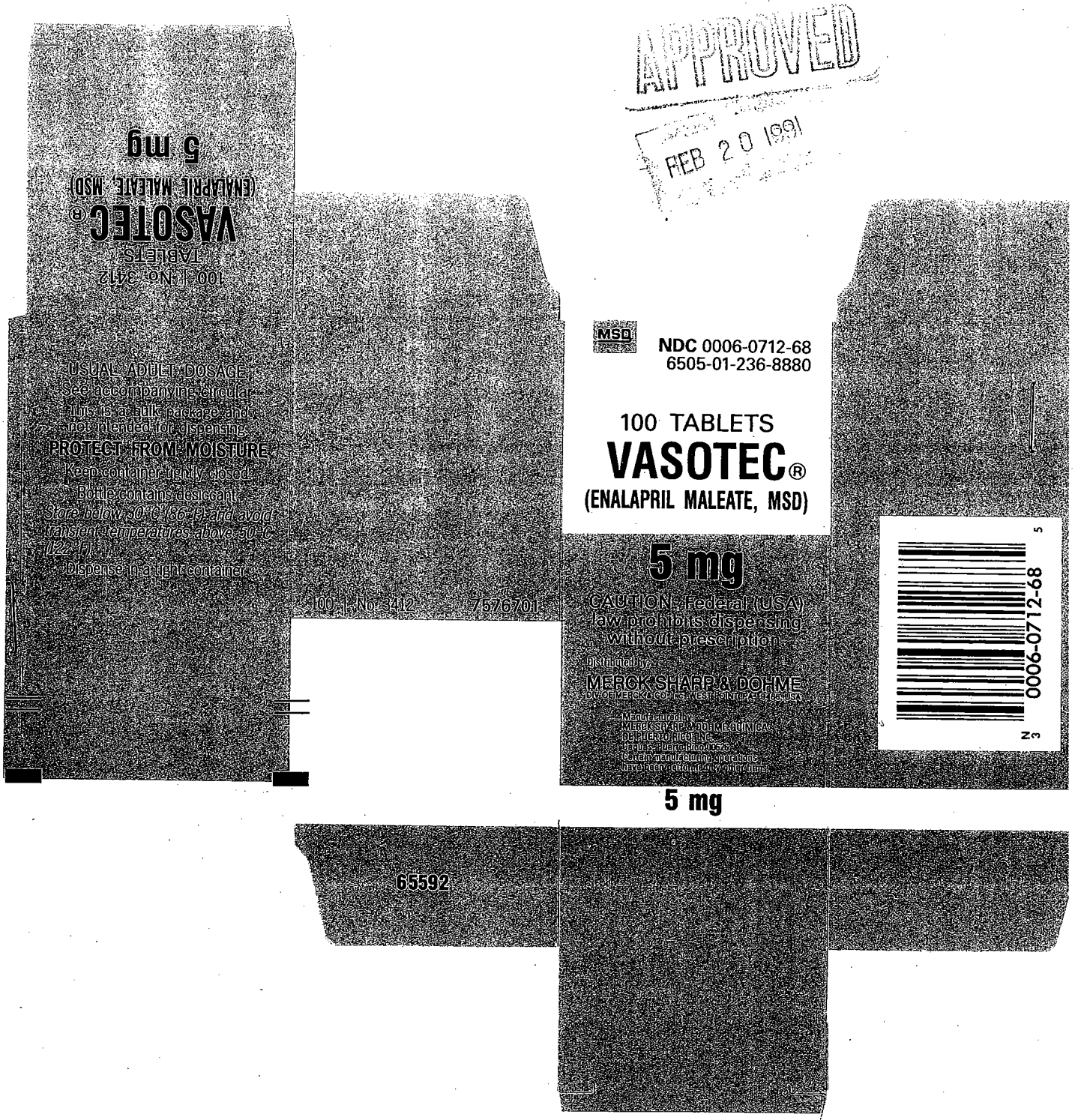
Issued December 1990

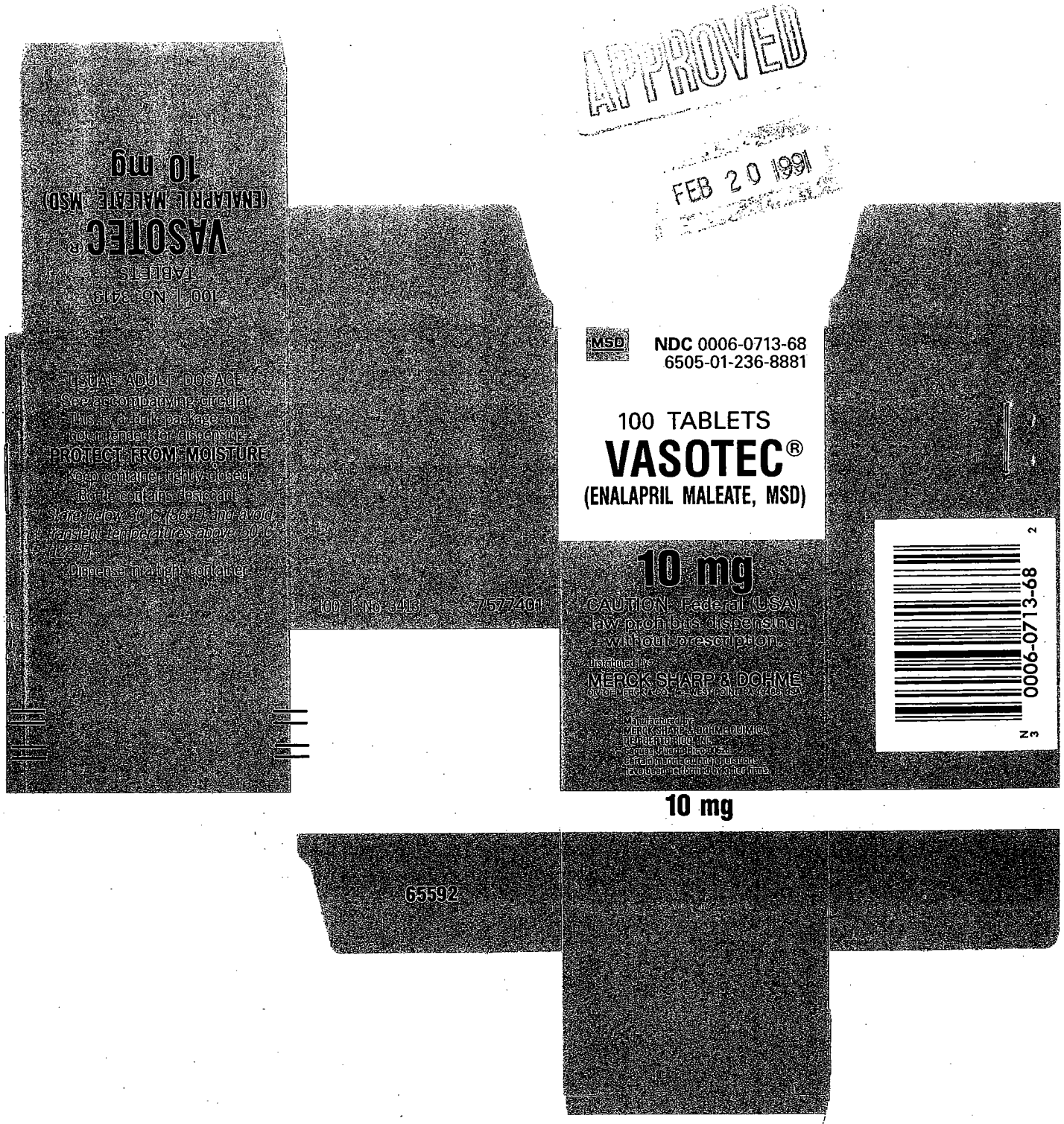
Printed in USA


APPROVED
FEB 20 1991
MSD
NDC 0006-0014-68
100 TABLETS
VASOTEC®
(ENALAPRIL MALEATE, MSD)
2.5 mg
CAUTION: Federal (USA) law prohibits dispensing without prescription.
Distributed by:
MERCK SHARP & DOHME
Manufactured by:
MERCK SHARP & DOHME QUIMICA
0006-0014-68
USUAL ADULT DOSAGE
See accompanying circular.
This is a bulk package and not intended for dispensing.
PROTECT FROM MOISTURE
Keep container tightly closed.
Bottle contains desiccant.
Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F).
Dispense in a tight container.
100 | No. 3411
7712100
VASOTEC®
(ENALAPRIL MALEATE, MSD)
TABLETS
100 | No. 3411
2.5 mg
65592

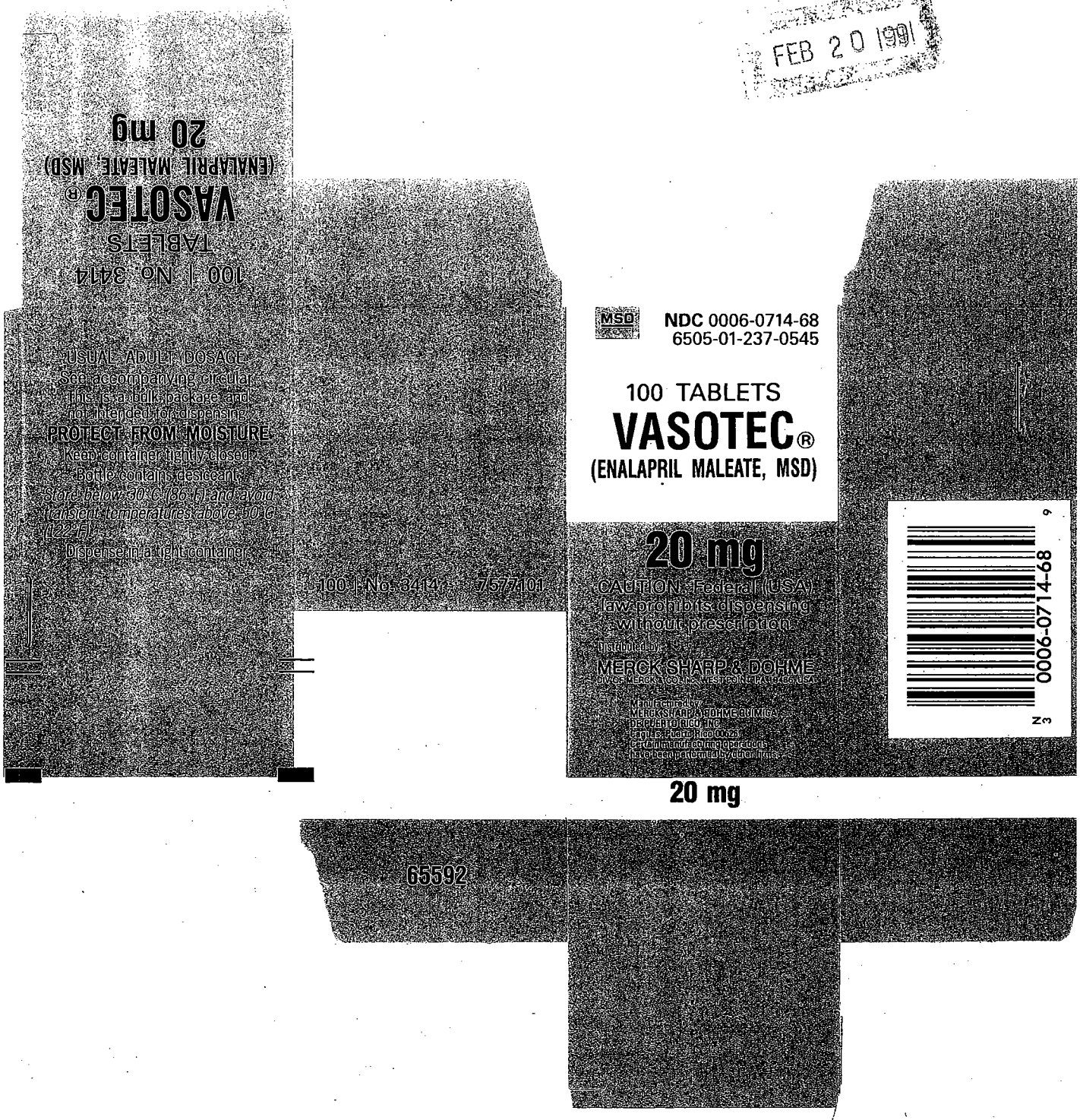
2.5 mg

APPROVED
FEB 20 1991



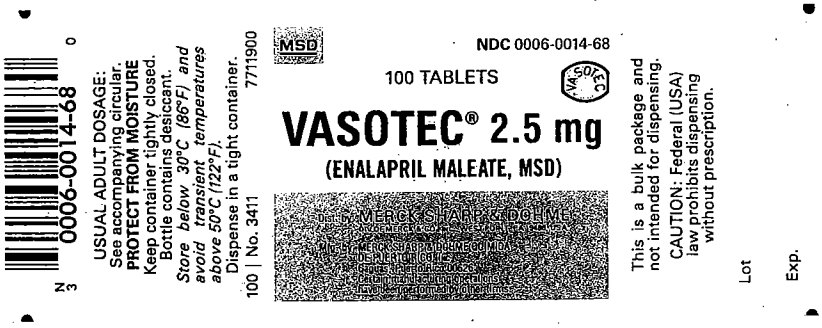

APPROVED
FEB 20 1991
MSD
NDC 0006-0713-68
6505-01-236-8881
100 TABLETS
VASOTEC®
(ENALAPRIL MALEATE, MSD)
10 mg
CAUTION: Federal (USA) law prohibits dispensing without prescription.
Distributed by:
MERCK SHARP & DOHME
0006-0713-68
10 mg
65592
7577401
100 | No. 3413
USUAL ADULT DOSAGE
See accompanying circular.
This is a bulk package and not intended for dispensing.
PROTECT FROM MOISTURE
Keep container tightly closed.
Bottle contains desiccant.
Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F).
Dispense in tight container.
100 | No. 3413
VASOTEC®
(ENALAPRIL MALEATE, MSD)
10 mg

APPROVED
FEB 20 1991



APPROVED

FEB 20 1991



APPROVED
FEB 20 1991

0006-0712-68

USUAL ADULT DOSAGE:
See accompanying circular.
PROTECT FROM MOISTURE
Keep container tightly closed.
Bottle contains desiccant.
Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F).
Dispense in a tight container.
100 | No. 3412 7576501

MSD

NDC 0006-0712-68

100 TABLETS

VASOTEC

VASOTEC® 5 mg
(ENALAPRIL MALEATE, MSD)

MERCK SHARP & DOHME

This is a bulk package and not intended for dispensing.
CAUTION: Federal (USA) law prohibits dispensing without prescription.

Lot

Exp.

APPROVED

FEB 20 1991

USUAL ADULT DOSAGE:
See accompanying circular.
PROTECT FROM MOISTURE
Keep container tightly closed.
Bottle contains desiccant.
Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F).
Dispense in a tight container.

MSD

NDC 0006-0713-68 100 | No. 3413

100 TABLETS

VASOTEC® 10 mg

(ENALAPRIL MALEATE, MSD)

MERCK SHARP & DOHME

This is a bulk package and not intended for dispensing.
CAUTION: Federal (USA) law prohibits dispensing without prescription.

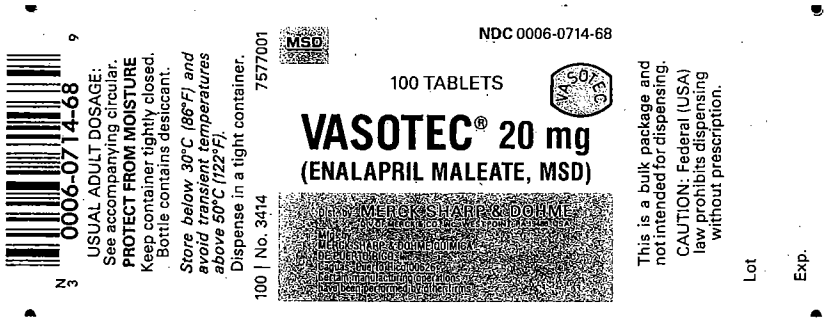
7577301

Lot

Exp.

APPROVED

FEB 20 1991



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S017

CHEMISTRY REVIEW(S)

FEB 19 1991

CHEMIST'S REVIEW	1. ORGANIZATION FDA/HFD-110	2. NDA NUMBER 18-998
3. NAME AND ADDRESS OF APPLICANT (City and State) MSD West Point, PA 19486		4. AF NUMBER
		5. SUPPLEMENT(S) NUMBER(S): S-017 DATE(S): 1/31/89
6. NAME OF DRUG Vasotec Tablets	7. NONPROPRIETARY NAME Enalapril Maleate	
8. SUPPLEMENTS(S) PROVIDES FOR: The manufacture of Tablets Vasotec in the MSD facilities in Caguas, PR at a site leased from MOVA.		9. AMENDMENTS AND OTHER DATES
10. PHARMACOLOGICAL CATEGORY No change	11. HOW DISPENSED [X] Rx [ ] OTC	12. RELATED IND/ NDA/DMF(s) SCM (2/11/91)
13. DOSAGE FORM(S) Tablets	14. POTENCY(IES) No change	
15. CHEMICAL NAME AND STRUCTURE No change		16 RECORDS/REPORTS CURRENT [ ] YES [ ] NO REVIEWED [ ] YES [ ] NO

17. COMMENTS

This is the final chemistry review related to S-017 which deals with FPL. The applicant had been sent an approvable letter dated 1/29/91.

The results of the requested inspection (date completed as 1/22/91) showed an approval action - see chemist's file.

The use of draft labeling to reflect the proper corporate entity, Merck Sharp & Dohme Quimica de Puerto Rico, Inc., Caguas, Puerto Rico 006262, appears to be satisfactory.

Carton labeling is provided for all dosage strengths (ie, 2.5, 5, 10, 20 mg).

The immediate container labels indicate that the bottles of 100 tablets are considered to be bulk packages and not intended for dispensing. This is perhaps why bottles contain a desiccant.

Revisions for the package insert are clearly indicated on pages 10-14.
STS #69

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend an approval action and have the chemist write the action letter.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Stuart Zimmerman	Stuart Zimmerman	2/14/91

DISTRIBUTION [X] ORIGINAL JACKET [ ] REVIEWER [ ] DIVISION FILE [ ] CSO

clb/2/15/91/5013C

2-19-91

JAN 29 1991

58.1

CHEMIST'S REVIEW	1. ORGANIZATION FDA/HFD-110	2. NDA NUMBER 18-998
3. NAME AND ADDRESS OF APPLICANT (City and State) MSD West Point, PA 19486		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S): S-017 DATE(S): 1/31/89
6. NAME OF DRUG Vasotec Tablets	7. NONPROPRIETARY NAME Enalapril Maleate	
8. SUPPLEMENTS(S) PROVIDES FOR: The manufacture of Tablets Vasotec in the MSD facilities in Caguas, PR at a site leased from MOVA Pharmaceutical Corp.		9. AMENDMENTS AND OTHER DATES S/A 10/23/90 (STS #67) S/A 12/19/90 (STS #66)
10. PHARMACOLOGICAL CATEGORY No change	11. HOW DISPENSED |X| Rx |_| OTC	12. RELATED IND/ NDA/DMF(s)
13. DOSAGE FORM(S) Tablets	14. POTENCY(IES) No change	
15. CHEMICAL NAME AND STRUCTURE No change		16 RECORDS/REPORTS CURRENT |X| YES |_| NO REVIEWED |_| YES |_| NO

17. COMMENTS

This is the third of a series of Chemistry Reviews dealing with this supplemental change. Other reviews are as follows:

Submission Date	Chemist's Review Date
1/31/89 (Orig)	2/14/89 (STS #98)
7/24/90 (Resub)	8/14/90 (STS #57)

This current review serves to account for the previous submissions and evaluative interactions with indexing references.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend an approvable action and send a note to compliance for priority clearance of the GMP check. The CSO will compose the action letter since there is labeling involved.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Stuart Zimmerman		12/21/90

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R/D init: RWolters/12/26/90

clb/12/21/90/3391C

Chronology of Submissions/FDA Actions

Date	Comments
01/31/89	S-017 submitted to FDA (STS #98)
02/16/89	FDA Letter (Not Approvable)
04/20/90	Withdrawal submission (STS #50)
05/02/90	FDA withdrawal letter (CSO)
07/24/90	Resubmission (STS #57)
08/10/90	Request for GMP Check to HFD-320 (Erroneously entered as S-025)
09/28/90	Request for GMP Check made by HFD-320 to HFR-SE500
10/23/90	Supplemental Amendment STS #67 dealing with the ——— held by MPMD Caguas ———
12/19/90	Supplemental amendment which provides stability data and draft labeling as requested by FDA (STS #66).

Chronology of Interactions

08/02/90	Record of conversation with Dr. Berger of MSD.
08/16/90	Memorandum of telephone conversation with Ms. Braxton (Drug Listing Branch of FDA).
12/06/90	Memorandum of telephone conversation with Dr. Berger of MSD.
12/06/90	Talk with Jim Donnie (FDA, San Juan).
12/07/90	Memorandum of telephone conversation with Dr. Berger of MSD.
12/07/90	Conversation with Ms. Mary Mason (FDA, San Juan).
12/17/90	Memorandum from Stuart Zimmerman to David Haggard, San Juan DO (Provided as Attachment I).

Stability Evaluation (Submission: 12/19/90):

Stability data is given for batches manufactured at Caguas with reference to batches manufactured at Wilson as a control. Results of accelerated testing show that the profiles for degradation across these compared sites are compatible; that is, the ——— This is seen for both the 2.5 mg/tablet and the 20 mg/tablet. The physical characteristics (color, appearance, etc.) remain satisfactory. These results can be reasonably interpolated to the total range of tablet sizes to be marketed.

Labeling: Satisfactory for the draft labeling submitted in the submission dated 12/19/90. Labeling is provided for the 5 mg, 10 mg, and 20 mg size tablets. This includes reference to the fact that the product will be manufactured by Merck Sharp & Dohme, Caguas, PR, Inc. The NDC number of 0006-712-68 corresponds to the code used by MSD for products associated with the domestic address of MSD at West Point, PA. No bar code is utilized by MSD. The submission indicates that the FPL for the 2.5 mg tablets will accompany the rest of the labeling after receipt of the approvable letter from FDA.

GMP Check: Satisfactory - as voiced by telephone.

An inspection was conducted by FDA, San Juan PR (DO) and in order to help facilitate the proper interpretations for the outcome results, I faxed a Memorandum dated 12/17/90 to both Mr. David Haggard (San Juan DO) and Ms. Carol Broadnax, Acting Chief of HFD-320 explaining the scientific circumstances involved. This is given in this review as Attachment I. Mr. Haggard mentioned that based on this memorandum he would issue an approval action to compliance.

———— Evaluation: Satisfactory for this proposed change.

———————————————————— Included are corrections concerning the specific areas which are dedicated to be used by MSD.

Concerning the identification of the equipment, it has been noted that additional information is necessary to be provided in the next DMF revision. This includes: (1) a full description of how the product history (e.g., across different drug products to guard against contamination potentials) of any particular piece of equipment can be traced; (2) model numbers and code numbers; (3) capacity factors; (4) potential for substitution between manufacturing applications in terms of compatible performance. I mentioned some of these things to Mr. Ramos and to Ms. Smith and they said they would take these matters under advisement for possible future updating/revisions.

———— Evaluation:

Concerning the evaluation of ———— it should be noted that it is intended to partially fill the requirements of Section 505(b)(4) for all of MSD's New Drug Applications. It contains general descriptions of the relevant facilities, methods of handling and controls for the manufacturing and processing of drug products.

Concerning the applicant's general need to submit a separate DMF covering their operations at MOVA, it is noted that ————————————————————

————————————————————

————————————————————

Owing to the general nature of the information provided, it is not considered necessary to evaluate all aspects of the control procedures given since the most critical controls are covered by the NDA 18-998 for Enalapril Maleate. Hence, only selected categories will be considered which more directly relate to this NDA.

Letters of Authorization:

Letters are provided for FDA to refer to the following DMFs in connection with this proposed change:

(1) ——— MSD/CAGUAS, P.R.
(Letter dated 12/30/87)

(2) ——— MOVA Pharmaceutical Corp., Caguas, PR
(Letter dated 12/18/87)

Environmental Assessment:

Concerning an environmental assessment, it is mentioned that MSD - Caguas will conduct operations in accordance with all local and/or Federal regulations and a statement will be included as part of each specific NDA pertaining to that NDA product.

Concerning the completeness of the applicant's ——— it should be noted that no attention is given to the particular code numbers of the pieces of equipment to be used in the operation. Under Section F (p. 10), general types of equipment are cited together with their corresponding suppliers. It may be considered to be an improvement to have the code numbers linked to these types. This would help provide more of an assurance that potential incompatibility problems would not result in the event that an alternately used piece of equipment was to be used on a substitutable basis. The capacity of each piece of equipment could also be given to help assure that there were no potential incompatibility concerns. These same kinds of evaluative concerns were addressed to ——— informal basis. I mentioned these matters to Dr. Elliot Berger on 12/19/90 and he said he would check out the feasibility of having these matters documented.

AUG 14 1990 18-998 56.1. 7.24-A.0 S-017 RS

CHEMIST'S REVIEW (If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
	18-998

3. NAME AND ADDRESS OF APPLICANT (City and State)
Merck Sharp and Dohme
West Point, Pennsylvania- 19486

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-017	1/31/89

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Vasotec Tablets	Enalapril Maleate

8. SUPPLEMENT(S) PROVIDES FOR:
the manufacture of Tablets Vasotec in the MSD facilites in Caguas, PR at a site leased from MOVA Pharmaceutical Corp.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
Resubmission to S-13 (7/24/90)

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED
No change	☒ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S)	14. POTENCY (Iso)
Tablets	No change

15. CHEMICAL NAME AND STRUCTURE
No change

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
Evaluative Comments are found in the following records of telephone conversations:

Date	Contact Person(s)	Firm(s)
8/6/90	Dr. E. Berger	MSD
8/2/90	" " "	"
8/9/90	Alvin Lopez	MSD at MOVA
	Eduardo Ramos	MOVA representative
8/9/90	Alvin Lopez	MSD at MOVA

STS# 57

18. CONCLUSIONS AND RECOMMENDATIONS
Consider this a preliminary review awaiting the results of an inspection request made on 8/10/90 and a response from the applicant about the letter of authorization from MOVA.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Stuart Zimmerman		8/14/90

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE ☐ CSO

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

FEB 16 1989

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA NUMBER 18-998
3. NAME AND ADDRESS OF APPLICANT (City and State) MSD West Point, Pennsylvania 19486		4. AF NUMBER 4-715 5. SUPPLEMENT(S) NUMBER(S): S-017 DATE(S): 1/31/89
6. NAME OF DRUG Vasotec	7. NONPROPRIETARY NAME Enalapril Maleate	
8. SUPPLEMENTS(S) PROVIDES FOR: Manufacturing tablets Vasotex by Merck Sharp and Dohme Caguas, A Division of Merck Sharp & Dohme Quimica de Puerto Rico, Inc. at MOVA Pharmaceutical Corporation in Caguas, Puerto Rico.		9. AMENDMENTS AND OTHER DATES
10. PHARMACOLOGICAL CATEGORY Antihypertensive (ACE)	11. HOW DISPENSED |X| Rx |_| OTC	12. RELATED IND/ NDA/DMF(s) _____
13. DOSAGE FORM(S) Tablets	14. POTENCY(IES) 2.5, 5, 10, 20 mg/tab	
15. CHEMICAL NAME AND STRUCTURE		16 RECORDS/REPORTS CURRENT | | YES | | NO REVIEWED | | YES | | NO

17. COMMENTS

This supplemental change is similar to the one that was submitted for _____ on _____ - refer to STS #76 in Chemist's Notes. In this case the firm was requested to provide comparative dissolution rate testing data as mentioned in our letter of _____ We should also require a disapproval in the present case based on the same reasons.

This supplement is an extension of the one provided June 17, 1988 (S-013) that dealt with the question of packaging Tablets VASOTEC by Merck Sharp & Dohme Caguas, a Division of Merck Sharp & Dohme Quimica de Puerto Rico, Inc. at a site leased from MOVA Pharmaceutical Corporation in Caguas, Puerto Rico. This S-013 was approved August 3, 1988.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend disapproval based on lack of comparative dissolution rate data.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Stuart Zimmerman	Stuart Zimmerman	2/14/89

DISTRIBUTION | √ | ORIGINAL JACKET | | REVIEWER | DIVISION FILE | | CSO

R/D init: RWolters/2/16/89

clb/2/14/89/1370C

Comments (continued)

Manufacturing and Processing: Satisfactory.

The manufacturing process and ingredients used will be the same as those already approved in the NDA. Reference is made to ——— for procedures used by MOVA Pharmaceutical Corporation in Caguas, Puerto Rico. This DMF has already been evaluated with respect to the review of S-013 (NDA 18-998) - refer to Chemist's Review dated 7/8/88 for details.

Stability: Satisfactory.

The applicant makes the commitment to place market samples from three early production lots produced ——— into the ongoing stability program and report the results to FDA in Annual Reports. Subpotent lots will be withdrawn from the market.

Establishment Inspection: Pending Status.

The subject facility has received a satisfactory CGMP inspection within the previous two years. The most recent inspection was conducted in association with a supplemental NDA ———————————————————

For another reference to a supplement that relates to the use of this site please refer to S-013 for NDA 18-998 dated 6/17/88. Chemist's Review #1 is filed under STS #72. This deals with ——————————————————— This supplement was approved on August 3, 1988. A GMP check was found to be acceptable as of 7/22/88.

In view of the need for additional information concerning the dissolution rate test for this product it is not considered necessary to request a GMP check at this time. One will be requested if and when the applicant provides a response to the current FDA deficiencies.

Bioavailability: Not entirely satisfactory.

The firm requests a waiver from the requirements to demonstrate the bioavailability of the Tablets VASOTEC in accord with 21 CFR 320.22(e). Since it is current FDA policy to have this decision take place it is not necessary to request the Division of Biopharmaceutics for a waiver. Also, it is not necessary to send HFD-2525 a memorandum regarding whether this is done or not. It is current policy to require - at the Division Level - that the applicant provide comparative dissolution testing data. The reference lot need not be the initially obtained bio-lot. Also, it was decided that this comparison need not be represented by three different batches.

This testing is to be considered to be adequate enough if the applicant employs just one lot since just an uninvolved check is desired. Nothing is to be expressed about whether pilot size lot is to be satisfactory; this will be based on what the applicant decides. Of course, a full sized manufacturing lot is preferable - but not mandatory.

10-998
5b.1

AUG 14 1990

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFD-110	18-998

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Merck Sharp and Dohme
West Point, Pennsylvania 19486

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-017 RS	7/24/90

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Vasotec Tablets	Enalapril Maleate

8. SUPPLEMENT(S) PROVIDES FOR:
the manufacture of Tablets Vasotec in the MSD facilites in Caguas, PR at a site leased from MOVA Pharmaceutical Corp.

9. AMENDMENTS AND OTHER *(Reports, etc.)* **DATES**

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED
No change	☒ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S)	14. POTENCY *(Iea)*
Tablets	No change

15. CHEMICAL NAME AND STRUCTURE
No change

16. RECORDS AND REPORTS
CURRENT ☐ YES ☐ NO
REVIEWED ☐ YES ☐ NO

17. COMMENTS
Evaluative Comments are found in the following records of telephone conversations:

Date	Contact Person(s)	Firm(s)
8/6/90	Dr. E. Berger	MSD
8/2/90	" " "	"
8/9/90	Alvin Lopez	MSD at MOVA
	Eduardo Ramos	MOVA representative
8/9/90	Alvin Lopez	MSD at MOVA

18. CONCLUSIONS AND RECOMMENDATIONS
Consider this a preliminary review awaiting the results of an inspection request made on 8/10/90 and a response from the applicant about the letter of authorization from MOVA.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Stuart Zimmerman		7/14/90

DISTRIBUTION ☒ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE ☐ CSO

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

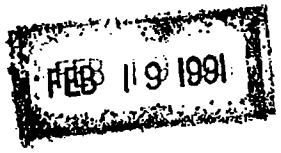
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CSO Review of Labeling



NDA 18-998/S-017

Date of submission: January 31, 1989

Withdrawal request: April 20, 1990 Withdrawal date: May 2, 1990

Date of resubmission: July 24, 1990

Amendments: October 23, 1990
December 19, 1990
February 11, 1991

Applicant: Merck Sharp & Dohme

Drug Name: Vasotec (enalapril maleate) Tablets

Date of Review: February 14, 1991

This supplemental application provides for an alternate site for the manufacture and control of the dosage form by Merck Sharp and Dohme, Caguas, Division of Merck Sharp and Dohme, Quimica de Puerto Rico, Inc., Caguas, Puerto Rico (MPMD Caguas) at a dedicated site leased from MOVA Pharmaceutical Corporation, Caguas, Puerto Rico.

Merck submitted final printed labeling in response to a January 29, 1991 approvable letter from Robert J. Wolters, Ph.D. The final printed labeling differs from the submitted draft labeling in the company designated as the manufacturer, which now is called Merck Sharp and Dohme Quimica de Puerto Rico, Inc., Caguas, Puerto Rico 00626. The final printed package insert contains the following changes:

The company signature has been changed from:

MSD, Merck Sharp & Dohme
Div. of Merck & Co., West Point, PA 19486, USA

to:
Distributed by:
MSD, Merck Sharp & Dohme
Div. of Merck & Co., West Point, PA 19486, USA

Manufactured by:
Merck Sharp and Dohme Quimica de Puerto Rico, Inc.
Caguas, Puerto Rico 00626
Certain manufacturing operations
have been performed by other firms.

Conclusion:
The submitted final printed labeling differs from the submitted draft labeling in that the company designation has been revised.

Under 21 CFR 5.80 (d)(1), the supervisory chemists in the divisions in ODE I are authorized to approve supplements that provide for a change in the labeling of the drug that reflects only the use of a different facility or establishment. Dr. Wolters has agreed to the changes; I will sign off on the final printed labeling and forward the volumes to him for the preparation of the approval letter.

Kathleen Bongiovanni

cc: NDA 18-998/S-017
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/2/14/91.

APR 4 1990

NDA 18-998/S-017

Merck Sharp & Dohme Research Laboratories
Attention: Elliott T. Berger, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Berger:

Please refer to your January 31, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Vasotec (enalapril maleate, MSD) Tablets.

The supplemental application provided for an alternate site of manufacturing and controls of the dosage form by Merck Sharp & Dohme Quimica de Puerto Rico, Inc., at a site leased from the NOVA Pharmaceutical Corporation in Caguas, Puerto Rico.

We also refer to our letter of February 16, 1989 notifying you that your supplemental application was not approvable. Your March 1, 1989 correspondence informed us of your intent to file an amendment to your application. A notice of intent to file an amendment constitutes an agreement by you to extend the review period under 21 CFR 314.60.

We have no record that you have filed an amendment fully responsive to our February 16 letter. Since over a year has passed, we will consider this supplemental application withdrawn under 21 CFR 314.120(a) unless you file such an amendment within thirty (30) days. Alternatively, you may wish to withdraw this supplement to your NDA under 21 CFR 314.65. Withdrawal would not prejudice any future resubmission of the supplemental application. You may request that the information in the withdrawn supplemental application be considered in conjunction with any resubmission.

We are concerned about improving our management of NDAs during the review process. Supplemental applications such as this, overburden our document rooms and distort our workload assignments. We, therefore, hope for your cooperation.

Sincerely yours,

mam 4/4/90

Natalia A. Morganstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/SBenton/4/4/90/5254S

INFORMATION REQUEST

4/14/90

MAY 2 1990

NDA 18-998/S-017

Merck Sharp & Dohme Research Laboratories
Attention: Elliott T. Berger, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Berger:

We acknowledge the receipt of your April 20, 1990 communication requesting withdrawal of your January 31, 1989 supplemental new drug application for Vasotec (enalapril maleate) Tablets.

The supplemental application provided for manufacturing of the dosage form by Merck Sharp & Dohme Quimica de Puerto Rico, Inc., at a site leased from the NOVA Pharmaceutical Corporation in Cuaguas, Puerto Rico.

In compliance with your request and in accord with 21 CFR 314.65, the supplemental application with respect to this preparation is regarded withdrawn. This withdrawal does not prejudice any future filing of this application. You may request that the information in this supplemental application you have withdrawn be considered in connection with any resubmission.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Nam 5/2/90
Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/KBongiovanni
sb 4/25/90;5/1/90/5324S
R/D: SZimmerman/4/30/90
RWalters/5/1/90
NMorgenstern/5/1/90

K. Bongiovanni 5-1-90

WITHDRAWN

8 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

NDA 18-998/S-017

FEB 16 1989

Merck Sharp & Dohme Research Laboratories
Attention: Elliott T. Berger, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Berger:

Please refer to your January 31, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate, MSD) Tablets.

This supplemental application provides for an alternate site of manufacturing and controls of the dosage form by Merck Sharp & Dohme Quimica de Puerto Rico, Inc., at a site leased from the MOVA Pharmaceutical Corporation in Caguas, Puerto Rico.

We have completed our review and find the information is inadequate and the supplemental application is not approvable under section 505(b)(1) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

> Comparative dissolution data should be furnished where at least 12 units have been tested on products manufactured at the newly proposed site with the NDA's approved dissolution method, and the products must meet the NDA's dissolution standard. Dissolution data on both the high and the low strengths of tablets should be provided in your case where you provide for a range of different strengths. Additionally, we request data that shows the complete dissolution profile using enough sample points to adequately cover the total release of the drug.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may withdraw this supplemental application.

Sincerely yours,

RW 2-16-89

Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/Rose
HFD-110/Wolters
HFD-110/Zimmerman/2/14/89
gl:2/14/89:r1:2/14/89/13690

Draft Init: RWolters/2/16/89

Stewart Zimmerman 2/16/89