CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-901/S-028

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	✓			
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Final Printed Labeling	✓			
Medical Review(s)	✓			
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER:
19-901/S-028

Trade Name: Altace™ Capsules

Generic Name: Ramipril

Sponsor: King Pharmaceuticals, Inc.

Approval Date: October 4, 2000

Indication(s): For reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes

Food and Drug Administration
Rockville MD 20857

NDA 19-901/S-028

OCT 4 2000

King Pharmaceuticals, Inc.
Attention: Mr. Thomas K. Rogers, III
501 Fifth Street
Bristol, Tennessee 37620

Dear Mr. Rogers:

Please refer to your supplemental new drug application dated January 14, 2000, received January 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Altace (ramipril) 1.25, 2.5, 5, and 10 mg Capsules.

We acknowledge receipt of your submissions dated January 18 and 31, February 4, 7, 17, and 26, March 9, 10 (two), and 27, April 19 and 20, May 11, July 17, September 26 (two), 27, and 28, 2000.

This supplemental new drug application provides for the new use of Altace Capsules for reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert included in your September 28, 2000 submission).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-901/S-128." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are **waiving** the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

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

If you have any questions, please call:

Ms. Sandra L. Birdsong
Regulatory Project Manager
(301) 594-5312

Sincerely,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-901/S-028

FINAL PRINTED LABELING

LEGEND

DRAFT LABELING

SPONSOR'S DRAFT LABELING

REVISED ACCORDING TO

SEPTEMBER 28, 2000 LABELING MEETING

Prescribing information as of September 2000

ALTACE® Capsules

(ramipril)

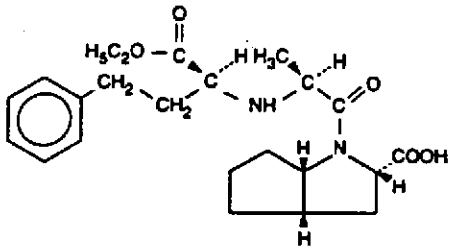
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE® should be discontinued as soon as possible. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

DESCRIPTION

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105° C and 112°C.

The CAS Registry Number is 87333-19-5. Ramipril's chemical name is (2*S*,3a*S*,6a*S*)-1[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]octahydrocyclopenta [*b*]pyrrole-2-carboxylic acid, 1-ethyl ester; its structural formula is:



Its empiric formula is C23H32N2O5, and its molecular weight is 416.5.

Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group.

ALTACE (ramipril) is supplied as hard shell capsules for oral administration containing 1.25 mg, 2.5 mg, 5 mg, and 10 mg of ramipril. The inactive ingredients present are pregelatinized starch NF, gelatin, and titanium dioxide. The 1.25 mg capsule shell contains yellow iron oxide, the 2.5 mg

capsule shell contains D&C yellow #10 and FD&C red #40, the 5 mg capsule shell contains FD&C blue #1 and FD&C red #40, and the 10 mg capsule shell contains FD&C blue #1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ramipril and ramiprilat inhibit 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. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with ALTACE alone for up to 56 weeks, approximately 4% of patients during the trial had an abnormally high serum potassium and an increase from baseline greater than 0.75 mEq/L, and none of the patients had an abnormally low potassium and a decrease from baseline greater than 0.75 mEq/L. In the same study, approximately 2% of patients treated with ALTACE and hydrochlorothiazide for up to 56 weeks had abnormally high potassium values and an increase from baseline of 0.75 mEq/L or greater, and approximately 2% had abnormally low values and decreases from baseline of 0.75 mEq/L or greater. (See **PRECAUTIONS**.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

The effect of ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma. 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 ALTACE remains to be elucidated.

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

Pharmacokinetics and Metabolism

Following oral administration of ALTACE, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.

In a trial in which subjects received ALTACE capsules or the contents of identical capsules dissolved in water, dissolved in apple juice, or suspended in apple sauce, serum ramiprilat levels were essentially unrelated to the use or nonuse of the concomitant liquid or food.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%; *in vitro*, these percentages are independent of concentration over the range of 0.01 to 10µg/ml.

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ramipril, about 60% of the parent drug and its metabolites is eliminated in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug, however the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the 2.5-20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9-18 hours. The terminal elimina-

tion phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation kinetics of the ramiprilat/ACE complex. It does not contribute to the accumulation of the drug.

After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13-17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ALTACE, especially at low doses (2.5 mg), but the difference is clinically insignificant.

In patients with creatinine clearance less than 40 ml/min/1.73m2, peak levels of ramiprilat are approximately doubled, and trough levels may be as much as quintupled. In multiple-dose regimens, the total exposure to ramiprilat (AUC) in these patients is 3-4 times as large as it is in patients with normal renal function who receive similar doses.

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 ml/min/1.73m2 had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations. (See **DOSAGE AND ADMINISTRATION**.)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat appears to be slowed, possibly because of diminished activity of hepatic esterases, and plasma ramipril levels in these patients are increased about 3-fold. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function, and the effect of a given dose on plasma ACE activity does not vary with hepatic function.

Pharmacodynamics

Single doses of ramipril of 2.5-20 mg produce approximately 60-80% inhibition of ACE activity 4 hours after dosing with approximately 40-60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes.

The Heart Outcomes Prevention Evaluation study (HOPE study) was a large, multi-center, randomized, placebo controlled, 2x2 factorial design, double-blind study conducted in 9541 patients (4645 on ALTACE) who were 55 years or older and considered at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that was accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). Patients were either normotensive or under treatment with other antihypertensive agents. Patients were excluded if they had clinical heart failure or were known to have a low ejection fraction (<0.40). This study was designed to examine the long-term (mean of five years) effects of ALTACE (10 mg orally once a day) on the combined endpoint of myocardial infarction, stroke or death from cardiovascular causes.

The HOPE study results showed that ALTACE (10 mg/day) significantly reduced the rate of myocardial infarction, stroke or death from cardiovascular causes (651/4645 *vs.* 826/4652, relative risk 0.78), as well as the rates of the 3 components of the combined endpoint.

Outcome	Altace (N=4645) no. (%)	Placebo (N=4652)	Relative Risk (95% CI) P value
Combined End-point			
(MI, stroke, or death from CV cause)	651 (14.0%)	826 (17.8%)	0.78 (0.70-0.86), P=0.0001
Component End-point			
Death from Cardiovascular Causes	282 (6.1%)	377 (8.1%)	0.74 (0.64-0.87), P=0.0002
Myocardial infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70-0.90), P=0.0003
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56-0.84), P=0.0002
Overall Mortality			
(Death from any Cause)	482 (10.4%)	569 (12.2%)	0.84 (0.75-0.95), P=0.005

This effect was evident after about one year of treatment.

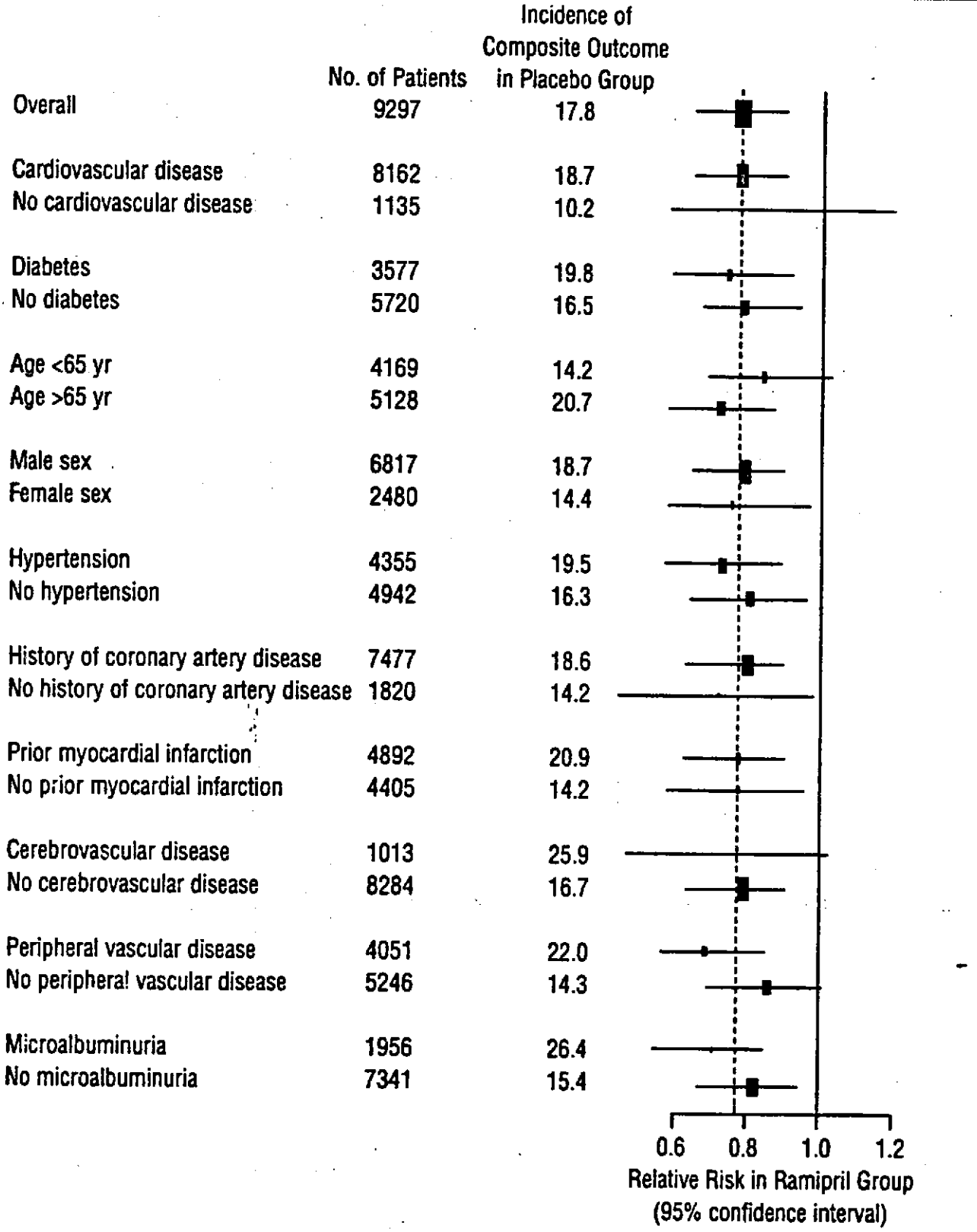


Figure 2. The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Subgroups. Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is proportional to the number of patients in each group. The dashed line indicates overall relative risk.

The benefits of ALTACE were observed among patients who were taking aspirin or other anti-platelet agents, beta-blockers, and lipid-lowering agents as well as diuretics and calcium channel blockers.

Hypertension

Administration of ALTACE to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See **WARNINGS.**) Use of ALTACE in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5-20 mg of ALTACE lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4-12 weeks) controlled studies, once-daily doses of 2.5-10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mm Hg more than placebo. In comparisons of peak vs. trough effect, the trough effect represented about 50-60% of the peak response. In a titration study comparing divided (bid) vs. qd treatment, the divided regimen was superior, indicating that for some patients the antihypertensive effect with once-daily dosing is not adequately maintained. (See **DOSAGE AND ADMINISTRATION.**)

In most trials, the antihypertensive effect of ALTACE increased during the first several weeks of repeated measurements. The antihypertensive effect of ALTACE has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ALTACE has not resulted in a rapid increase in blood pressure.

ALTACE has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and as atenolol. In both caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril.

Except for thiazides, no formal interaction studies of ramipril with other antihypertensive agents have been carried out. Limited experience in controlled and uncontrolled trials combining ramipril with a calcium channel blocker, a loop diuretic, or triple therapy (beta-blocker, vasodilator, and a

diuretic) indicate no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

ALTACE was less effective in blacks than in caucasians. The effectiveness of ALTACE was not influenced by age, sex, or weight.

In a baseline controlled study of 10 patients with mild essential hypertension, blood pressure reduction was accompanied by a 15% increase in renal blood flow. In healthy volunteers, glomerular filtration rate was unchanged.

Heart Failure Post Myocardial Infarction

ALTACE was studied in the Acute Infarction Ramipril Efficacy (AIRE) trial. This was a multinational (mainly European) 161-center, 2006-patient, double-blind, randomized, parallel-group study comparing ALTACE to placebo in stable patients, 2-9 days after an acute myocardial infarction (MI), who had shown clinical signs of congestive heart failure (CHF) at any time after the MI. Patients in severe (NYHA class IV) heart failure, patients with unstable angina, patients with heart failure of congenital or valvular etiology, and patients with contraindications to ACE inhibitors were all excluded. The majority of patients had received thrombolytic therapy at the time of the index infarction, and the average time between infarction and initiation of treatment was 5 days.

Patients randomized to ramipril treatment were given an initial dose of 2.5 mg twice daily. If the initial regimen caused undue hypotension, the dose was reduced to 1.25 mg, but in either event doses were titrated upward (as tolerated) to a target regimen (achieved in 77% of patients randomized to ramipril) of 5 mg twice daily. Patients were then followed for an average of 15 months (range 6-46). The use of ALTACE was associated with a 27% reduction ($p=0.002$), in the risk of death from any cause; about 90% of the deaths that occurred were cardiovascular, mainly sudden death. The risks of progression to severe heart failure and of CHF-related hospitalization were also reduced, by 23% ($p=0.017$) and 26% ($p=0.011$), respectively. The benefits of ALTACE therapy were seen in both genders, and they were not affected by the exact timing of the initiation of therapy, but older patients may have had a greater benefit than those under 65. The benefits were seen in patients on, and not on, various concomitant medications; at the time of randomization these included

aspirin (about 80% of patients), diuretics (about 60%), organic nitrates (about 55%), beta-blockers (about 20%), calcium channel blockers (about 15%), and digoxin (about 12%).

INDICATIONS AND USAGE

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

Altace is indicated in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. Altace can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

Hypertension

ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, 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. Available data are insufficient to show that ALTACE does not have a similar risk. (See **WARNINGS**.)

In considering use of ALTACE, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. (See **WARNINGS, Angioedema**.)

Heart Failure Post Myocardial Infarction

Ramipril is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure. (See **CLINICAL PHARMACOLOGY, Heart Failure Post Myocardial Infarction** for details and limitations of the survival trial.)

CONTRAINDICATIONS

ALTACE 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.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ALTACE) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also **CONTRAINDICATIONS**.)

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered. (See ADVERSE REACTIONS.)**

In a large U.S. postmarketing study, angioedema (defined as reports of angio, face, larynx, tongue, or throat edema) was reported in 3/1523 (0.20%) of black patients and in 8/8680 (0.09%) of white patients. These rates were not different statistically.

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor.

Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension

ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

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 such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of

White blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure 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. Exchange transfusion or dialysis m. y be required as means of reversing hypotension and/or substituting for disordered renal functio . ALTACE which crosses the placenta can be removed from the neonatal circulation by these ne ns, but limited experience has not shown that such removal is central to the treatment of thes infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, an cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 00 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

PRECAUTIONS

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-ald sterone system, changes in renal function may be anticipated in susceptible individuals. In pat nts with severe congestive heart failure whose renal function may depend on the activity of he renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inh bitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rare) with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases i blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin con rting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation f ALTACE and/or diuretic therapy. In such patients renal function should be monitored during he first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal v scular disease have developed increases in blood urea nitrogen and serum creatinine, usually min r and transient, especially when ALTACE has been given concomitantly with a diuretic. This is mo re likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE a d/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of rena function.

(See **DOSAGE AND ADMINISTRATION.**)

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 m q/L) occurred in approximately 1% of hypertensive patients receiving ALTACE (ramipril). In most ases, these

were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. 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 ALTACE. (See **DRUG INTERACTIONS**.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

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

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syn-

cope occurs, ALTACE should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

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

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

Drug Interactions

With diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced. (See **DOSAGE AND ADMINISTRATION**.)

With potassium supplements and potassium-sparing diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ALTACE and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of ALTACE and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of ALTACE with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For either species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Nursing Mothers

Ingestion of single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ALTACE should not breast feed.

Geriatric Use

Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypertension

ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE, only asthenia (fatigue) was more common on Altace than placebo (2% vs. 1%).

PATIENTS IN US PLACEBO CONTROLLED STUDIES

	ALTACE (n=651)		Placebo (n=286)	
	n	%	n	%
Asthenia (Fatigue)	13	2	2	1

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of patients requiring discontinuation of treatment.

Heart Failure Post Myocardial Infarction

Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients and more frequently on ramipril are

shown below. The incidences represent the experiences from the AIRE study. The follow-up time was between 6 and 46 months for this study.

Percentage of Patients with Adverse Events Possibly/Probably Related to Study Drug

Placebo-Controlled (AIRE) Mortality Study

Adverse Event	Ramipril (n=1004)	Placebo (n=982)
Hypotension	11	5
Cough Increased	8	4
Dizziness	4	3
Angina Pectoris	3	2
Nausea	2	1
Postural Hypotension	2	1
Syncope	2	1
Vomiting	2	0.5
Vertigo	2	0.7
Abnormal Kidney Function	1	0.5
Diarrhea	1	0.4

HOPE Study:

Safety data in the HOPE trial were collected as reasons for discontinuation or temporary interruption of treatment. The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials (see WARNINGS).

	RAMIPRIL (N=4645) %	PLACEBO (N=4652) %
Discontinuation at any time	34	32
Permanent discontinuation	29	28
Reasons for stopping		
Cough	7	2
Hypotension or Dizziness	1.9	1.5
Angioedema	0.3	0.1

Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain); events not likely to be drug related and minor events have been omitted.

Body As a Whole: Anaphylactoid reactions. (See **WARNINGS**.)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (See **WARNINGS** and **PRECAUTIONS**), syncope and palpitations.

Hematologic: Pancytopenia, hemolytic anemia and thrombocytopenia.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See **WARNINGS**.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See **WARNINGS**.)

Gastrointestinal: Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, increased salivation and taste disturbance.

Dermatologic: Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), erythema multiforme, pemphigus, photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Miscellaneous: As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported.

Fetal/Neonatal Morbidity and Mortality. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings:

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of

patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See **WARNINGS** and **PRECAUTIONS**.) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See **WARNINGS** and **PRECAUTIONS**.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE

Single oral doses in rats and mice of 10-11 g/kg resulted in significant lethality. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Limited data on human overdosage are available. The most likely clinical manifestations would be symptoms attributable to hypotension. Laboratory determinations of serum levels of ramipril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of ramipril overdose. No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of ramipril and its metabolites. Similarly, it is not known which, if any, of these substances can be usefully removed from the body by hemodialysis. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of ramipril

overdose, but angiotensin II is essentially unavailable outside of scattered research facilities.

Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Blood pressure decreases associated with any dose of ALTACE® depend, in part, on the presence or absence of volume depletion (e.g., past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, the initial starting dose should be 1.25 mg once daily.

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

ALTACE® should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently post myocardial infarction, it can also be given as a divided dose.

Hypertension

The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally 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 ALTACE alone, a diuretic can be added.

Heart Failure Post Myocardial Infarction

For the treatment of post-infarction patients who have shown signs of congestive failure, the recommended starting dose of ALTACE is 2.5 mg twice daily (5 mg per day). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily, and after one week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.

After the initial dose of ALTACE, 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 any concomitant diuretic

should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ALTACE does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The ALTACE Capsule is usually swallowed whole. The ALTACE Capsule can also be opened and the contents sprinkled on a small amount (about 4 oz.) of apple sauce or mixed in 4 oz. (120 ml) of water or apple juice. To be sure that ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration.

Concomitant administration of ALTACE with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See **PRECAUTIONS.**)

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ALTACE. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with ALTACE. (See **WARNINGS.**) Then, if blood pressure is not controlled with ALTACE alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used to avoid excess hypotension.

Dosage Adjustment in Renal Impairment

In patients with creatinine clearance <40 ml/min/1.73m² (serum creatinine approximately >2.5 mg/dl) doses only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat. (See **CLINICAL PHARMACOLOGY.**)

Hypertension: For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

Heart Failure Post Myocardial Infarction: For patients with heart failure and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. The dose may be increased to 1.25 mg b.i.d. and up to a maximum dose of 2.5 mg b.i.d. depending upon clinical response and tolerability.

HOW SUPPLIED

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in hard gelatin capsules, packaged in bottles of 100 capsules. ALTACE is also supplied in blister packages (10 capsules/blister card).

ALTACE 1.25 mg capsules are supplied as yellow, hard gelatin capsules in bottles of 100 (NDC 61570-110-01), and Unit Dose packs of 100 (NDC 61570-110-56).

ALTACE 2.5 mg capsules are supplied as orange, hard gelatin capsules in bottles of 100 (NDC 61570-111-01), and Unit Dose packs of 100 (NDC 61570-111-56).

ALTACE 5 mg capsules are supplied as red, hard gelatin capsules in bottles of 100 (NDC 61570-112-01), and Unit Dose packs of 100 (NDC 61570-112-56).

ALTACE 10 mg capsules are supplied as Process Blue, hard gelatin capsules in bottles of 100 (NDC 61570-120-01).

Dispense in well-closed container with safety closure.

Store at controlled room temperature (59 to 86° F).

Rx only.

Prescribing Information as of September 2000

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620

Manufactured by: Aventis Pharmaceuticals Inc., Kansas City, MO 64137

Monarch Pharmaceuticals®

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-901/S-028

MEDICAL/STATISTICAL REVIEWS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
Division of Cardio-Renal Drug Products

Public Health Service

Memorandum

DATE : May 16, 2000

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 19-901, S-028, Ramipril for high-risk patients, King Pharmaceuticals, Inc.

TO : Director, Office of Drug Evaluation 1, HFD-110

Introduction

The Heart Outcomes Prevention Evaluation (HOPE) study was a large, simple, factorial trial that compared the effects of ramipril (titrated to the maximum approved dose) and Vitamin E to placebo in a double blind, factorial design. Only the results of the ramipril vs. placebo are submitted to this NDA. There were 9541 patients randomized (4645 to 10 mg ramipril, 4652 to placebo (and 244 to 2.5 mg of ramipril; not reported to the NDA). Only 8 patients were lost to follow-up, the remainder are all accounted for. Remarkable for a study that cost only in the vicinity $1000 per patient reported (in contrast to several thousand dollars per patient).

A protocol existed in August, 1993 (but, the final protocol is dated March 21, 1994), the study began in December, 1993, the study was terminated by the Data and Safety Monitoring Committee in March, 1999 (final study visits being June 30, 1999), this supplement was submitted January 12, 2000, the major result of HOPE was published in the N.E.J.M. on January 20, 2000, the major FDA combined Medical/Statistical review was completed April 3, 2000 (with several addenda, later), the Cardiac and Renal Drugs Advisory Committee met to discuss the results of HOPE on May 1, 2000. From study start to end was 6.5 years, first analysis took 3 to 4 months, from end of study to submission (and publications) took 9.5 months, and FDA time to the date of this memorandum has been 5 months.

The Randomized Patient Population

Inclusion Criteria

The protocol states "A wide range of high risk patients". This was defined as in the final protocol:

1) Women and men aged 55 or above at high risk of developing a major cardiovascular event.

A. Coronary disease: Previous myocardial infarction, stable or unstable angina with documented multivessel coronary disease or positive stress (ST depression greater than or equal to 2 mm or positive thallium), or multivessel PTCA (patients can be entered into Run-in Phase one week after these events but should only be randomized one month after these events), multivessel CABG (more than 4 years ago or with anginal or multivessel coronary disease* seen on angiography.*
**multivessel coronary artery disease is defined as >50% stenosis in at least two major coronary arteries*

B. Other patients at high risk of developing MI or stroke:
C.

*(I) **Peripheral vascular disease**: Previous limb bypass surgery or percutaneous transluminal angioplasty, previous limb or foot amputation, history of intermittent claudication with ankle/arm blood pressure ratio of 0.80 or lower in at least one side, significant stenosis (>50%) documented by angiography.*

*(II) **Previous stroke** (more than one month ago).*

(III) **Diabetes** *(insulin-dependent or non-insulin dependent) with one of the following cardiovascular risk factors: hypertension, (BP >160 mm Hg systolic or > 90 mm Hg diastolic or on treatment); total cholesterol > 5.2 mal/L (>200 mg/dl); HDL cholesterol , 0.9 mmol/l (3.5 mg/dl); current cigarette smoking; known microalbuminuria or any evidence of previous vascular disease.*

Exclusion Criteria

Relate primarily to absolute indicatic~s or contra-indications for the use of ACE-I or Vitamin E and to the presence of other medical problems that would either interfere with participation in the trial or lead to the inability to complete the trial.

1) *Drug use: Current use of ACE-I (e.g., for heart failure, EF < 40% or severe hypertension) or current use of Vitamin E and inability to discontinue these medications; or known hypersensitivity to ACE-I or Vitamin E.*

2) *Cardiovascular diseases*

    1) *Ejection Fraction < 40% (only if known)*
    2) *Hemodynamicaly significant primary valvular or outflow tract obstruction (e.g., mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve).*
    3) *Constrictive pericarditis.*
    4) *Complex congenital heart disease.*
    5) *Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion).*
    6) *Planned cardiac surgery or angioplasty within 3 months (patient may be reconsidered for the trial after the procedure).*
    7) *Uncontrolled hypertension.*
    8) *Cor Pulmonale.*
    9) *Heart transplant recipient.*
    10)

3) *Other conditions*

    1) *Significant renal disease defined as:*
        a) *renal artery stenosis;*
        b) *creatinine clearance < 0.6 ml/second or serum creatinine >200 mEq/L (2.26 mg/dl);*
        c) *overt nephropathy: >= 1 plus proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hrs);*
        d) *hyperkalemia; K > 5.5 mEq/l.*

    2) *Any other major non-cardiac illness expected to reduce life expectancy of interfere with study participation.*

    3) *Patient is simultaneously taking another experimental drug.*

    4) *Previously randomized to HOPE.*

During the Advisory Committee meeting, Dr. Yusuf stated that at the time of randomization, all patients were asymptomatic with respect to cardiovascular disease. This was not a correct statement, since patients could have had angina, intermittent claudication, etc. What was meant was that the patients were essentially stable, with high risk factors and chronic diseases.

The Major Result

The **primary endpoint** was the combination of cardiovascular death, myocardial infarction and stroke. There were 651 (14.0%) such events in the ramipril group and 826 (17.8%) such events in the placebo group; the point estimate for hazard ratio was 0.78. This was statistically significant, favoring ramipril (p = 0.0001).

Other major analyses

For the combination of all-cause death, myocardial infarction and stroke, there were 822 (17.7%) such events in the ramipril group and 992 (21.3%) such events in the placebo group; the point estimate for hazard ratio was 0.81. This was statistically significant, favoring ramipril (p = 0.0001).

For **all-cause death alone** (not a pre-specified end-point) there were 482 (10.4%) events in the ramipril group and 569 (12.2%) events in the placebo group, hazard ratio 0.84 (p = 0.005). This is a rather striking finding, favoring ramipril.

There is not much else to say here. The trial, by any criterion I could imagine, clearly found a benefit of ramipril when treating patients who were stable but at high risk of having cardiovascular events.

Are there things to worry about ?

Not many, but some.

Revascularization

This was a pre-specified secondary end-point. There were 743 (16.0%) events in the ramipril group and 854 (18.4%) events in the placebo group, hazard ratio 0.86 (p = 0.002). These were any kind of revascularization, elective, emergency, etc., not just "urgent revascularizations". The trial was a blinded trial, so it is unlikely that systematic bias played a role, but in the past we have been rather specific, requiring "urgent revascularizations" and excluded elective procedures from serious thought.

The incidence of myocardial infarction was decreased by ramipril treatment (hazard ratio 0.80, p = 0.0003), but the incidence of hospitalization for "unstable angina" (also a prespecified secondary outcome) was dead even (554 events in the ramipril group and 567 events in the placebo group), as was worsening angina (1010 events in the ramipril group and 1117 events in the placebo group), as was hospitalization for unstable angina with ECG changes (175 events in the ramipril group and 180 events in the placebo group). It is not clear to me how to interpret the decrease in revascularizations and the other events together. Could it be that a *p* of 0.002 for a prespecified end-point was a play of chance ?

I get even more puzzled when looking at the myocardial infarction database. Patients who had a myocardial infarction and had symptoms were fewer in the ramipril group (383, 83.4%) than in the placebo group (472, 82.8%). So, with an acute event, patients were equally symptomatic.

If ramipril treatment altered the progression of atherosclerosis (a natural interpretation from the major trial result, and decreased the incidence of myocardial infarction and decreased the incidence of stroke [the latter two being statistically significant on their own]), the decreased need for myocardial revascularization would be an expected finding. Why then did the incidence of unstable angina **not** track the expected, not even what could be called a lean ?

I cannot even speculate. Certainly even in a highly significant trial, inferences from multiple analyses are usually not appropriate. I don't know the answer here, but I favor not having the revascularization finding in labeling. Simply because it has different meaning from that which is in current labeling for other approved drugs and I cannot think of the words that would appropriately clarify the meaning in this labeling vs. other labeling.

Diabetes

This could be long section, with long discussion. I will keep it brief.

Nothing special about diabetes should go into this labeling. Like the entire HOPE population, diabetics receive the same treatment benefit of ramipril. There is no reason to single them out in labeling, despite there being a substudy that had statistically significant findings as well.

The finding that fewer new diagnoses of diabetes were found in the ramipril treated group (3.6%) than in the placebo group (5.4%), hazard ration 0.66 (p0.001), was a retrospective analysis finding and as said by Dr. Yussef at the Advisory Committee meeting raises a hypothesis that is worth testing again (at least once more).

The albuminuria, nephropathy, microvascular effects can be argued about for many hours. I am comfortable that, like many other ACEI ramipril decreases the progression of albuminuria compared to placebo. Thus far, we have not settled for that as a claim for anything.

The single placebo controlled trial in insulin dependent diabetic patients that measured "hard end-points" is the trial that supported approval of captopril (Lewis, et.al., N.E.J.M. 1993;320: 1456-62). The principal endpoint in that trial was doubling of the serum creatinine (captopril won, p = 0.007) and there was a secondary endpoint of death/dialysis/transplantation (captopril won here too, p = 0.006). In the Lewis, et. al. trial, microalbuminuria was also decreased by captopril (p = 0.001).

In non-diabetic renal disease patients there is also a single trial (3 publications from the Gruppo Italiano di Studi Epidemiologici in Nefrologia [a trial with the acronym REIN for Ramipril Efficacy In Nephropathy]). There is also a link between albuminuria and "hard endpoints". The link is weaker (complicated, but p values for treatment effects favoring ramipril usually have on only one 0 after the decimal point.

Strangely, there is not a mention of serum creatinine in our reviews, nor is there a mention of serum creatinine in the HOPE publications, nor is there a mention of serum creatinine in anything the sponsor wrote. I am not requesting it from anyone. I say this to simply state that it missing from my document also. I do not think I would be swayed one way or the other by knowing the numbers.

Canada vs. USA

Although this was discussed, it is fairly easy to deal with. It is an original by FDA non-prespecified subgroup analysis (in fact Dr. Yusuf said he would not even dream of performing such an analysis), it leans in the right direction and the US population represented is small compared to the total randomized patients. This is not worthy of discussion.

Dosing and Administration

For hypertension the current labeling says the recommended starting dose is 2.5 mg once-a-day. It then says one should titrate and before adding another drug try administering trice-a-day (keeping the total daily dose at 10

mg). So it is a once or twice-a-day antihypertensive.

For heart failure post myocardial infarction current labeling says always give twice-a-day. One might think that was in recognition of the fact that the hemodynamic effects, in some patients, do not last for an entire inter-dosing interval, as reflected in the antihypertensive dosing recommendations. Not so. This reflects the study that resulted in approval, the study administered ramipril twice-a-day; no ifs, ands or buts. That study also found a 27% ($p = 0.002$) reduction in the risk of death from any cause.

So, it is clear that in one population at high risk (patients with heart failure after myocardial infarction, twice-a-day dosing resulted in a reduction of death from any cause. It is also clear that twice-a-day dosing is more appropriate in some patients, for the control of hypertension.

Along comes HOPE. Ramipril was dosed once daily in HOPE. Does this mean that a person now receiving ramipril for the treatment of hypertension twice-a-day should be switched to once-a-day ? I think the answer is clearly not to switch to once-a-day, if twice-a-day is controlling the blood pressure reasonably.

Since the hypertension trials did not measure anything other than blood pressure, should one ignore that ramipril can reasonably be given twice-a-day? Again, I think the answer is clearly not. Not all patients being treated with ramipril for hypertension have to be on a once-a-day regimen, from the fear of not getting a mortality benefit.

So, what to do ? It seems odd to break from the empirical tradition of always doing exactly what the trial did, but I think it is reasonable to do so here. I would recommend that for all 3 indications, the language be x mg per day, in single or 2 divided doses. That is exactly what the hypertension labeling says, it is different from the post myocardial infarction trial and it different from the HOPE trial. I think there is good clinical trial data that says ramipril decreases all cause mortality (and presumably all the other things) in either single or divided dose. I also think that for blood pressure, the antihypertensive effect wanes during a once-a-day dosing interval.

My suggestion would read as follows:

DOSAGE AND ADMINISTRATION

For all indicated uses ALTACE^R doses are specified as total daily dose. It may be administered once or twice a day, depending upon the response. For hypertension, 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. Blood pressure decreases associated with any dose of ALTACE^R depend, in part, on the presence or absence of volume depletion (e.g., past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, the initial starting dose should be 1.25 mg.

Reduction of myocardial infarction, stroke and death in high risk patients

The starting dose of ALTACE^R should be 2.5 mg per day. After one week, the dose should be increased to 5 mg (if tolerated) and then 3 weeks later increased to 10 mg per day (if tolerated).). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily, and after one week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 10 mg per day, with dosage increases being about 3 weeks apart. The maximum blood pressure lowering from any dose takes 2 to 4 weeks to be manifest.

Hypertension

The recommended initial dose for patients not receiving a diuretic is 2.5 mg per day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day. If blood pressure is not controlled after several weeks of 10 mg ALTACE^R administered twice a day (total daily dose of 20 mg), a diuretic can be added.

Heart Failure post myocardial infarction.

For the treatment of post-infarction patients who have shown signs of congestive heart failure, the recommended starting dose of ALTACE^{R} is 2.5 mg twice daily (5 mg per day). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily, and after one week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 10 mg per day, with dosage increases being about 3 weeks apart.

After the initial dose of ALTACE^{R}, 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 any concomitant diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ALTACE^{R} does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

Other factors to consider

The ALTACE^{R} Capsule is usually swallowed whole. The ALTACER Capsule can also be opened and the contents sprinkled on a small amount (about 4 oz.) of applesauce or mixed in a 4 oz. (120 ml) of water or apple juice. To be sure that ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration.

AND THEN IT GOES ON AS IS (the last heading "Other factors to consider" is new, the words that follow it are as they currently are in the package insert).

Hope

Canadian Cardiovascular Collaboration
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April 20, 2000

To:

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April 20, 2000

Dr. R. Lipicky MD
Director, Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: Altace NDA 19-901, S-028
Combined Medical & Statistical Review
Heart Outcomes Prevention Evaluation Study (HOPE)
Division of Cardio-Renal Drugs, HFD-110
April 3, 2000

Dear Dr. Lipicky:

As promised please find enclosed the list of additional issues that we noted from our review of the statistical and medical review. As Dr. Yusuf noted, these issues will not have an effect on any outcome, however to ensure accuracy is maintained we wanted to bring these to your attention.

1. Page 7, 1st paragraph, Line 11. Please note that the DSMB rejected the primary use of formal stopping rules (i.e. used without consideration of all available evidence) and advised that emerging data be viewed within the context of all available evidence, including statistical considerations, so that any advice about stopping the trial would be based on a balance of risks and benefits.
2. Page 8. Please note that the following secondary endpoints are incorrectly identified:
   - acute ischemic cardiac syndromes (MI, unstable angina or severe angina requiring emergency coronary artery bypass surgery or angioplasty). This should read hospitalization for unstable angina only.
   - All cardiovascular revascularization procedures should read "all revascularization procedures".
   - the individual outcomes of the primary composite endpoint MI, stroke and cardiovascular death should all be listed here instead of just cardiovascular mortality.
3. Page 20, Patient Description incorrectly states that 1044 patients were excluded from randomization. 1035 patients were excluded from randomization.
4. Page 20, Table of Reasons for Rejection. This table seems to indicate a primary reason for patient withdrawal but centers were not asked for the primary reason for withdrawal and were encouraged to report all reasons for withdrawal for each patient.
5. Page 21, paragraph 2: 8 patients lost. We have only six patients lost and Janice Pogue had asked Dr. Targum to identify the two additional patients that you were counting so we may compare why there is a disrepancy.
6. Page 22, Protocol Violations and Deviations, Paragraph 2. No mention was made of the fact that the protocol violations was corrected, as noted in the DSMB minutes.
7. Page 23, Table 2.1 – Concomitant Medications at 2 year visit. The footnote indicates that the table was generated from visit 5, however the 2 year visit is visit 7. In addition, we

appear to have discrepancies throughout. Please see our analyses provided in Appendix A.

8. Page 24, Table 2.2: The line labeled as Antiplatelet agents really refers to "Other Antiplatelet Agents" and does not include the use of aspirin.
9. Page 25, Table 3. We believe the discrepancies between our numbers and yours on compliance can be explained by the fact that the denominator for compliance was taken out of the number of valid (i.e. including those who returned for a visit, had a telephone/home visit, answered the "stopping ramipril" question, and excluded patients who died). Also dose of ramipril was taken from the dose prescribed to be taken after the visit (where available) instead of daily dosage prior to the visit (where available). We have included our analyses in Appendix B.
10. Page 26, Table 4: Cardiovascular death confidence interval should read (0.64, 0.87).
11. Page 26, Table 5: The cause of death provided is as reported by center prior to adjudication. Please indicate this.
12. Page 27, Table 6: The following corrections should be made:
    Anterior Q waves ramipril;71, placebo 93
    Lateral Q waves ramipril: 12, placebo:12
    Inferior Q waves ramipril; 150, placebo: 166
    New Bundle Branch Block: ramipril 46, placebo 68
13. Page 28, Table 7: For the three secondary outcomes listed, hazard ratios and p values are discrepant in a minor way. Perhaps missing dates were not imputed as indicated in the database documentations.
14. Page 28, Table 7: Worsening angina values should be ramipril 1107(23.8%), placebo 1222(26.3%), CI 0.88(0.82-0.96), p=0.003.
15. Page 28, Table 7: Hosp for angina with ECG changes, number of events for placebo group is 180 and should be 181.
16. Page 29, Table 9: Vitamin E Grp: Cardiovascular death, MI, stroke should read; Hazard ratio: 0.79, CI: (0.68, 0.91), p=0.0009, no vitamin E grp: cardiovascular death, MI, stroke should read; Hazard ratio: 0.76, CI:(0.66, 0.89), p=0.0003.
17. Page 30, Subgroup results: 2nd line of paragraph is misleading and should not be included. The subgroup analyses by ethnicity and region are unreliable because of the relatively small numbers and potentially misleading. Furthermore tests for interactions are not presented and if done would be wholly non-significant.
18. Page 37, Table 18: Footnote to table, Definition of Type II diabetes: Should read "age of onset ≥30 or if younger than 30, not currently on insulin".
19. Page 37, Table 18: Stroke should read Stroke or TIA.
20. Page 37, Table 18: History of cardiovascular disease is undefined and we are unable to check the numbers until this is defined.
21. Page 38, Table 19. Same issues as noted in point 7 (issues around determination of those eligible for a visit and those patients on dose).
22. page 39, Table 20: Comparator group to female patients with diabetes should be male patients with diabetes.
23. Page 39, Table 21: As in point 13, perhaps missing dates were not imputed for the 3 secondary outcomes.
24. Page 41, Table 23: The comparison of the development of microalbuminuria must exclude patients who had the condition at baseline or randomization. Therefore this line should be ramipril 431/1256 (34.3%), placebo 451/1182 (38.2%), hazard ratio 0.93 (0.81, 1.06), p=0.28.
25. Page 41, Table 23: Doubling of creatinine from baseline at any visit after randomization. The numbers we have found are ramipril 41 (2.3%), and placebo 32 (1.8%), hazard ratio 1.24 (0.78, 1.97), p=0.36.
26. Page 40, Renal outcomes, 7th line. As noted in our letter of yesterday, the p-value should be 0.045. In addition, the suggestions for changes to Table 23 were made in the previous letter.
27. Page 42, Table 24: In light of the inaccuracies in Table 23, Table 24 is also incorrect.

28. Page 44, Serious Adverse Events, 2nd line: It is noted that the serious adverse events were not adjudicated. This statement is inaccurate as each serious adverse event was adjudicated.
29. Page 44, Footnote to Table 27: Although pt [redacted] did not have cancer indicated on the serious adverse event form, it was indicated that this patient had cancer on the patient summary form and this information was included in all cancer analyses.

We thank-you again for the opportunity to present these issues and we are please to hear that changes can be made to the report prior to it's publication on the web. Please do not hesitate to contact us if you have any questions regarding any of the above issues.

Yours truly.

Janice Pogue, MSc, MA
Statistician
HOPE Study

Jackie Bosch, MSc
Coordinator
HOPE Study

Cc: T. Rogers, King Pharmaceuticals
S. Yusuf

Appendix A

Concomitant Medications at 2 Years

	Ramipril Active		Ramipril Placebo	
	N	%	N	%
No. of 2 Yr Visits	4437	100.0	4451	100.0
Beta-blockers	1673	37.7	1802	40.5
Aspirin and Other Antiplatelets	3261	73.5	3330	74.8
Aspirin	3122	70.4	3192	71.7
Other Antiplatelet Drugs	210	4.7	216	4.9
Non-steroidal Anti-Inflammatory Agent	291	6.6	287	6.4
Oral Anticoagulants	245	5.5	229	5.1
Diuretics	738	16.6	854	19.2
Nitrates	1284	28.9	1359	30.5
Any Calcium Channel Blocker	1983	44.7	2006	45.1
Diltiazem/Verapamil	1026	23.1	1065	23.9
Other CCB	926	20.9	965	21.7
Cholesterol Lowering Agent	1691	38.1	1711	38.4
Vitamin C	254	5.7	242	5.4
Beta-carotene	43	1.0	36	0.8
Multivitamins	302	6.8	281	6.3
Estrogen(Females only)	130	10.7	155	13.7
Estrogen + Progesterone (Females only)	41	3.4	49	4.3
Insulin (Diabetics only)	556	12.7	586	13.3
Oral Hypoglycemic Drugs (Diabetics only)	963	22.0	977	22.2

Appendix B

B1: Summary of Number of Patients Taking Study Medication at Indicated Time Point

	Number of Patients (%)	
	Ramipril	
	Active	Placebo
Eligible at 1 yr**	4562	4562
On At 1 yr	3904 (85.5)	4072 (89.2)
On full dose study drug at 1 yr	3784 (82.9)	4014 (87.9)
On reduced dose study drug at 1 yr	120 (2.6)	58 (1.3)
Eligible at 2 yrs	4437	4451
On At 2 yrs	3603 (81.1)	3752 (84.3)
On full dose study drug at 2 yrs	3313 (74.6)	3594 (80.7)
On reduced dose study drug at 2 yrs	290 (6.5)	158 (3.5)
Eligible at 3 yrs	4336	4301
On At 3 yrs	3324 (76.6)	3420 (79.5)
On full dose study drug at 3 yrs	3077 (70.9)	3291 (76.5)
On reduced dose study drug at 3 yrs	247 (5.7)	129 (3.0)
Eligible at 4 yrs	3920	3854
On At 4 yrs	2652 (67.6)	2730 (70.8)
On full dose study drug at 4 yrs	2448 (62.4)	2623 (68.0)
On reduced dose study drug at 4 yrs	204 (5.2)	107 (2.8)

**number of patients alive and having completed the visit

B2: Summary of Number of Patients Taking Study Medication: Final Study Visit

	Number of Patients (%)	
	Ramipril	
	Active	Placebo
Eligible for Final Visit	4150	4070
On At Final Visit	2913 (70.2)	2958 (72.7)
On full dose study drug at Final Visit	2700 (65.1)	2854 (70.1)
On reduced dose study drug at Final Visit	213 (5.1)	104 (2.6)

APPENDIX B(CON'T)

B3: COMPLIANCE ADJUSTED FOR OPEN LABEL ACE-I USE
N (% of visit completed)

VISIT	RAMIPRIL ACTIVE						
	ELIGIBLE N	ON STUDY DRUG	ON OPEN LABEL ACE-I	TOTAL ON ANY ACTIVE ACE-I	ELIGIBLE N	RAMIPRIL PLACEBO ON OPEN LABEL ACE-I	CONTRAST %
1 YR	4565	3904 (85.5)	101 (2.2)	3988 (87.4)	4566	153 (3.4)	84.0
2YR	4440	3603 (81.1)	200 (4.5)	3773 (85.0)	4451	265 (6.0)	79.0
3 YR	4339	3324 (76.6)	256 (5.9)	3568 (82.2)	4302	347 (8.1)	74.1
4 YR	3923	2652 (67.6)	307 (7.8)	2946 (75.1)	3855	417 (10.8)	64.3
FINAL VISIT	4150	2913 (70.2)	392 (9.4)	3274 (78.9)	4070	501 (12.3)	66.6

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

Date: 04/30/2000
From: Shaw T. Chen, M.D., Medical Team Leader, HFD-110
To: Director, Division of Cardiorenal Drug Products, HFD-110
Director, Office of Drug Evaluation-I, HFD-100
Subject: NDA 19-901, S-028 Ramipril for reducing cardiovascular events in high risk patients, Approvability

OVERVIEW

This memorandum and the attached material constitute the Team Leader's recommendation that NDA 19-901 SE1-028, Altace (ramipril) for reducing cardiovascular events in high-risk patients, be approved. The *cardiovascular events* include cardiovascular deaths, myocardial infarction (MI) and stroke; *high risk* patients are defined as those who have vascular/coronary disease or those with diabetes and at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL, smoking or microalbuminuria).

The new efficacy claim is based on the results of a new trial, Heart Outcome Prevention Evaluation (HOPE), a randomized, double blind, placebo controlled, 4-year mortality/morbidity study. Results of the study have been presented in recent meetings and published in journals (*New Eng J Med*, 342:145-153, 154-160, 2000 and *The Lancet*, 355:253-259, 2000), reprints of which are enclosed. The history of development for the HOPE protocol and other background information have been summarized in the introductory sections of the Medical/Statistical Review. While the HOPE trial also evaluated the effects of vitamin E (see study design below), the Primary Review and this memo focussed only on the analyses of data related to ramipril.

This supplemental application has been reviewed jointly by Dr. Targum of the division and Dr. James Hung of Biometrics (their report is referred to as the Primary Review in this memo). Attached to their review is a brief summary of literatures on the use of angiotensin converting enzyme inhibitors (ACEi) in diabetic nephropathy, prepared by Dr. Throckmorton, also of this division. The sponsor did submit an information package for the Advisory Committee meeting of May 1, 2000, which is also included in this package. The HOPE data will be presented at that meeting and the application considered by the Advisory Committee. The Committee's final position will be reported in another memo by the Division.

It was decided in the filing meeting for this NDA supplement that no inspection of the clinical trial is necessary, provided that no serious treatment–center interaction is observe.

THE NEW CLAIMS

Based on the results of HOPE trial, the sponsor proposed the following new indication:

Prevention of myocardial infarction, stroke, and death from cardiovascular causes:

This draft, submitted in the briefing document of March 31, 2000 for the Advisory Committee, was revised slightly from an earlier version (*italic* type added or removed).

The new labeling also includes a description of the HOPE trial in the *Pharmacodynamics and Clinical effects* section, under the heading of Prevention of myocardial infarction, stroke, and death from cardiovascular causes.

THE HOPE PROTOCOL

As summarized by Drs. Targum and Hung in their review, the HOPE study was designed based on the premises that ACE inhibition reduces cardiovascular morbidity/mortality and is protective in patients at high risk for atherosclerosis. It is a large (9,000 patients), randomized, multi-center, double blind, parallel placebo controlled study with a 2 by 2 factorial design (ramipril, placebo by vitamin E, placebo) to evaluate the effects of 4- year treatment with ramipril and vitamin E.

Patients enrolled in HOPE must have vascular diseases (coronary, peripheral or stroke) or diabetes with at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL, smoking or microalbuminuria). They have thus some evidence of, or are at risk for, atherosclerotic diseases, but, unlike those of previous related ACEi studies, not necessarily hypertensive, with a recent documented infarction or in significant heart failure (actually, low left ventricular ejection fraction [<40%, if known] was excluded). For the diabetes substudy, patients were admitted regardless of their insulin dependence but should have no significant renal diseases (see exclusion criteria in Primary Review). The primary reviewers also questioned the classification of diabetes mellitus on the basis of age of onset and medication use, which was not clearly defined in protocol. But as long as both the insulin dependent and non-independent types were well-represented and distribution matched in all treatment groups, less precise diagnoses may approach more practical settings and only introduce noise, not bias.

Ramipril treatment was started at 2.5 mg and increased, over a 4-week period, to 10 mg once daily for maintenance. Patients were followed every 6 months for an average of 3.5 years (4 yrs planned).

In the original protocol, the **primary efficacy endpoint** is a combination of the following events (time to event analyses):

nonfatal MI,
nonfatal stroke,
death from cardiovascular cause (CV death)

In the above, cardiovascular death was defined as deaths due to MI, stroke, pulmonary emboli, arrhythmia or other cardiovascular events. Sudden deaths without any other documented causes were also included. Detailed definitions of other endpoints are referred to the Primary Review. During the development of the protocol, the Agency had some reservation about using cause specific death as a component of the primary endpoint. This concern was alleviated somewhat by the fact that similar effects were observed with all cause mortality (see results below).

There were 7 **secondary endpoints**, which include acute cardiac ischemic syndrome, all cardiovascular revascularization procedures, cardiovascular mortality, total deaths, development of overt nephropathy or dialysis in diabetic patients, hospitalization for heart failure, and cancer by site/morphology. The major events were subject to review by the Event Adjudication Committee, the extent of which was not clear, but probably beyond that specified in the protocol (i.e., not just discrepancies between hospital records or death certificates and case/event report forms, see Primary Review).

In addition to the same set of primary/secondary efficacy endpoints as that of the main study, the **diabetes substudy** also listed the following diabetes-specific secondary endpoints:

incipient diabetic nephropathy
progression from incipient to overt nephropathy
deterioration in renal function
glucose control (hemoglobin A1c)
diabetic retinopathy requiring laser surgery
rate of limb amputation and foot infection

Of these secondary endpoints in the diabetic substudy, some (e.g., glucose control, microalbuminuria, deterioration in renal function, and overt nephropathy) were either not well defined in protocol or with variable changes in different reports which were not submitted as protocol amendment.

During the trial, the protocol was amended with a number of revisions, which were summarized in the Primary Review (Pages 5-6). Except for those noted above, the great majority had no serious impact on integrity of the data or conclusion of the results.

EFFICACY RESULTS: MAIN STUDY

The results of the HOPE trial were published in two articles, one describing the main study (*New Eng J Med*, 342:145-153, 154-160, 2000) and the other paper contained the diabetic substudy (*The Lancet*, 355:253-259, 2000). Both of these publications have been summarized in the Primary Review and attached to this package.

In the main study, 4,652 were randomized to placebo and 4,645 to ramipril.10 mg. There were additional 244 patients who were assigned to 5 mg of ramipril and were excluded from

efficacy analyses. As described in the Primary Review, the treatment groups were well-matched in demographics, other baseline characteristics and concomitant medications.

Statistically, HOPE is a positive study with quite robust findings. The results of **primary efficacy endpoint** showed that ramipril is much more effective than placebo in reducing the predefined CV events with an impressive significance for the difference:

	Ramipril	placebo	hazard ratio	
Primary Endpoint	N=4645	N=4652	(95% CI)	p
CV death, MI or stroke	14.0%	17.8%	0.78 (0.70-0.86)	0.0001

While one may question the use of cause-specific mortality, the definition of CV death was reasonable (see above) and replacing it with all cause mortality led to similar result:

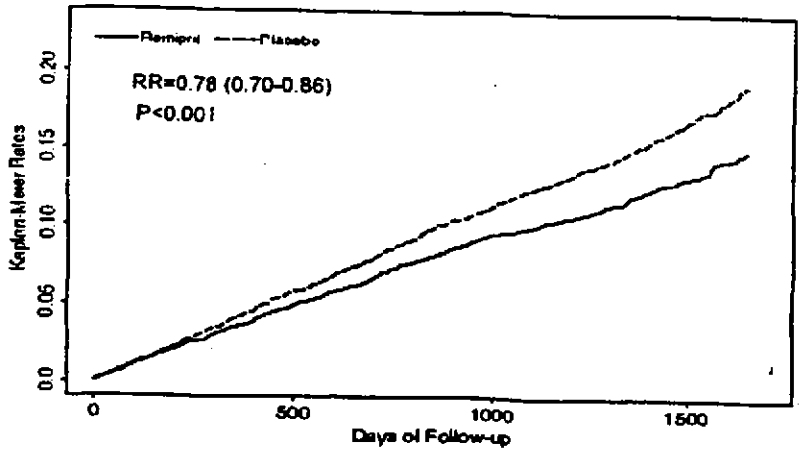
	Ramipril	placebo	hazard ratio	
	N=4645	N=4652	(95% CI)	p
all-cause death, MI or stroke	17.7%	21.3%	0.81 (0.74-0.89)	0.0001

Thus verifying causes of each death will probably not affect the study outcome and selective reviews of individual cases have not revealed any big surprise. Measurements in the components of the primary endpoint were also consistently in favor of ramipril with impressive significance:

	Ramipril	placebo	hazard ratio	
	N=4645	N=4652	(95% CI)	p
CV deaths	6.1%	8.1%	0.74 (0.64-0.87)	0.0002
MI	9.9%	12.3%	0.80 (0.70-0.90)	0.0003
stroke	3.4%	4.9%	0.68 (0.56-0.84)	0.0002
all-cause death	10.4%	12.2%	0.84 (0.75-0.95)	0.005

It is interesting to note that this is probably the first convincing piece of data showing ACEi reduced MI in these patients. As described in the Primary Review, the mortality effect of ramipril was independent of the terminal CV event (MI, stroke or arrhythmia, etc see Table 5 of Primary Review). There was no between group difference in non-CV deaths (4.3% ramipril vs 4.1% placebo, hazard ratio 1.03 with 95% CI 0.85-1.26, p=0.74).

The primary treatment effect was evident after about one year and persisted throughout follow up in the study, as shown by the survival curves in the following figure:



The reviewers also checked the censoring distribution for both the primary endpoints and the same primary set but replaced with all-cause mortality and concluded that the above efficacy analyses were valid (Appendix A of Primary Review). Thus, the morbidity/mortality benefits of ramipril treatment in patients at risk of atherosclerotic cardiovascular diseases appear to be well established in HOPE, with a quite robust finding in the primary endpoints.

Of the three pre-specified **secondary endpoints**, ramipril reduced revascularization, but not hospitalizations, either for unstable angina or heart failure (Table 7, Primary Review

Secondary Endpoints	Ramipril N=4645	placebo N=4652	hazard ratio (95% CI)	p
revascularization	16.0%	18.4%	0.86 (0.78-0.94)	0.002
hosp. unstable angina	11.9%	12.2%	0.97 (0.87-1.09)	0.65
hosp. for heart failure	3.0%	3.5%	0.87 (0.69-1.09)	0.22

The sponsor also claims that cardiac arrest, heart failure and worsening angina were decreased, but these endpoints were not pre-defined:

Non-prespecified Endpoints	Ramipril N=4645	placebo N=4652	hazard ratio (95% CI)	p
cardiac arrest	0.8%	1.3%	0.62 (0.41-0.94)	0.024
heart failure*	9.0%	11.5%	0.77 (0.68-0.87)	0.0001
worsening angina*	23.8%	26.3%	0.88 (0.82-0.96)	0.003

* check box on case report form

Efficacy results of the main study are independent of **vitamin E** treatment (Table 9 of Primary Review) and fairly consistent across different **patient subgroups** (Table 10 of Primary Review). Treatment effects of ramipril in a few demographic subgroups were with point estimates in the right direction but wide, non-significant confidence intervals, most likely due to small sample sizes (non-Caucasians, without CV diseases at baseline, and non-Canadian centers, Tables 12-17 of Primary Review). Ramipril was also beneficial regardless of baseline treatments with beta-blockers, calcium antagonists, diuretics, aspirin or other antiplatelet agents. As shown in Table 11 of the Primary Review, patients not receiving **aspirin** at baseline appeared to have a much greater reduction in primary endpoint events than those who were so treated, but this is not a comparison between randomized groups.

EFFICACY RESULTS: DIABETES RELATED CLAIMS

New Diabetes in the Main Study

In addition to the Diabetes Substudy (see below), the sponsor also analyzed the main study for **new diagnoses of diabetes mellitus** (DM) in patients who did not have DM at baseline. As shown in Table 8 of the Primary Review, ramipril treated patients had fewer new cases of DM over the course of the study:

	Ramipril N=2837	placebo N=2883	hazard ratio (95% CI)	p*
New cases of DM	3.6%	5.4%	0.66 (0.51-0.85)	0.001

* All deaths are censored at the time of death.

Note that this is not a pre-specified endpoint and as pointed out in the Primary Review (Page 29), this finding is independent of the primary endpoint and interpretation of the nominal p-value is difficult. Since *prevention of new onset of DM* in patients at risk for cardiovascular diseases is a totally brand new claim for ACEi with immense public health implication, an isolated, *post hoc* finding for ramipril without any external supporting data from other members of the class should not be considered as conclusive for approval of general use.

The Diabetes Substudy

There were total of 3,597 patients randomized in the diabetes substudy (1,808 to ramipril and 1,789 to placebo), with fairly well matched characteristics at baseline (Table 18 of Primary Review). Treatment effects of the primary endpoints were remarkably consistent with that of the main study:

Diabetes Substudy	Ramipril	placebo	hazard ratio	
Primary Endpoint	N=1808	N=1769	(95% CI)	p
CV death, MI or stroke	15.3%	19.8%	0.75 (0.64-0.88)	0.0004
CV deaths	6.2%	9.7%	0.63 (0.49-0.79)	0.0001
MI	10.2%	12.9%	0.78 (0.64-0.94)	0.01
stroke	4.2%	6.1%	0.67 (0.50-0.90)	0.0074

Again, the effect on total mortality in the substudy was also significant and the results of pre-defined secondary endpoints were very similar to that of the main study (only revascularization reached nominal significance, see Table 21 of Primary Review).

Beyond the same set of cardiovascular endpoints as the main study, the remaining results of the diabetes substudy were more problematic and difficult to interpret, as noted in the protocol description above and in the Primary Review.

For **control of hyperglycemia**, as measured by the adjusted mean changes from baseline in percentage of patients who had hemoglobin A_{1C} above upper limit of normal, ramipril appeared to be more effective in the first two years. But it seemed to become worse than the placebo afterwards (Table 22 of the Primary Review). Thus no conclusion can be reached on the potential benefit of ramipril to improve glucose control in diabetes.

In terms of the benefit of ramipril treatment on **renal function** in diabetes, the significance of the outcome was found to be sensitive to the definition of nephropathy endpoint used in the analyses. If the diagnosis of overt nephropathy was defined as in the HOPE protocol (reported at least in one of the yearly visits in the reviewers' analyses):

≥ 1+ proteinuria on dipstick, or

> 200 microgram/min (300 mg/24 hrs) urine albumin excretion

Ramipril was no different from placebo (Table 23R, Primary Review):

	Ramipril	placebo	hazard ratio	nominal
Diabetes Renal endpoint	N=1808	N=1769	(95% CI)	p
overt nephropathy (protocol)	13.8%	15.6%	0.86 (0.72-1.02)	0.075

When the endpoint was changed to the following, one with the smallest p value of the three different sets in the Lancet report,

albumin/creatinine ratio > 36 mg/mmol (without 24 hr urine data), or
≥ 500 mg/24 hr protein excretion, or
> 200 microgram/min (300 mg/24 hrs) albumin excretion

the result was more suggestive of a treatment effect, with a smaller nominal p value than that based on the protocol definition for overt nephropathy:

Diabetes Renal endpoint	Ramipril N=1808	placebo N=1769	hazard ratio (95% CI)	nominal p
overt nephropathy (Lancet)	6.8%	8.5%	0.78 (0.62-0.99)	0.045

For other endpoints related to **vascular/renal complications of diabetes**, ramipril did not improve in renal dialysis, laser surgery for retinopathy, microalbuminuria, or doubling of creatinine (see Table 23 of Primary Review). This may be due to low individual event rates, as retrospectively defined analyses using composite endpoints of these renal/vascular events suggest that ramipril may be beneficial (Table 24 of Primary Review):

Composite Endpoint* with:	Ramipril N=1808	placebo N=1769	hazard ratio (95% CI)	nominal p
overt nephropathy (protocol)	49.3%	52.8%	0.89 (0.81-0.98)	0.015
overt nephropathy (Lancet)	45.0%	49.8%	0.87 (0.79-0.96)	0.004

* overt nephropathy, laser surgery, renal dialysis, microalbuminuria & revascularization.

However, because the analyses were retrospective and the endpoint definitions were confusingly variable (see Primary Review), this finding can only serve as a new hypothesis for further investigation. The reviewers were thus not very convinced that ramipril reduces diabetes specific renal or vascular complications, except for the cardiovascular events as described above.

SAFETY DATA

There were no surprising safety problems in the HOPE trial. All adverse experiences were already known for the drug and more of tolerability rather than safety issues (see Tables 25-30, Primary Review). Cough was the adverse experience prominently more common in the ramipril group, leading to withdrawal in 7.3% of ramipril patients (vs 2% in placebo) in both the main study and diabetes substudy. Angioedema was not particularly frequent or severe in the HOPE trial. There was no other significant between-group imbalance in serious events, hospitalization for non-cardiovascular reasons, or discontinuation due to adverse events.

OVERALL ASSESSMENT

The reviewers all agree that the results of the main study are strongly positive and convincingly support the major claim of reducing cardiovascular death, MI and stroke in high risk patients as defined in the study. In contrast, the findings of secondary endpoints and the diabetes substudy were much less solid statistically and more difficult to interpret, but seemed

odd to be dismissed totally in view of totality of the data and external support. The regulatory issues are thus not so much related to approvability of the main efficacy claims, but instead concerning how extensive the benefits of ramipril treatment can be extracted from the HOPE data. The points of deliberation, therefore, are centered on the generalization of the patient population, validity of secondary endpoint benefits and diabetes related claims.

Patients Indicated to Treat

In HOPE, the patients must have history of vascular diseases or diabetes with additional risk factor(s) for atherosclerotic complications, but not necessarily hypertensive, symptomatic or suffering a recent MI and subjects with low left ventricular ejection fraction were excluded. Since the HOPE patients were of broader spectrum and in general less clinically ill than those in prior ACEi morbidity/mortality studies, the new indication represents a more preventive use of ACEi than previously accepted. As pointed out in the published report for HOPE (*New Eng J Med*, 342:145-153, 2000), ramipril was clearly beneficial in patients with preserved ventricular function and in those who had no history of MI. In this respect, it is noteworthy that HOPE was successful to show the effect of ramipril but SOLVD-Prevention had failed for enalapril.

Then there is the question of whether the HOPE protocol has a clinically meaningful definition of patient to be treated. One may ask if a "large and simple" trial like HOPE may be too inclusive to have admitted non-responsive (or even adversely affected) patients and further refining the patient selection may improve the treatment benefit. For instance, the reviewers were concerned that patients participated in the HOPE study are loosely defined in their diagnoses of underlying disorders (such as types of diabetes, see comments in Primary Review). Otherwise, however, conceivable subgroup analyses in HOPE have not generated hypotheses that ramipril should not be used in certain sub-populations*.

On the other hand, it is also possible that the entry criteria may be too artificially restrictive. They could be only instrumental to ensure selection of patients with high event rates (and success of the study), but the benefit of ramipril is actually applicable to a larger population with the same continuum of pathophysiology. While very few would accept this non-empirical argument without data, because of the impressive showing of the main study, it will be tempting to extend the applicability of HOPE experience in practice and start the ramipril therapy even earlier. That is, use in patients with some evidence of atherosclerosis but less additional risk factors than those specified in the trial (e.g., high cholesterol without history of vascular disease or diabetes without additional risks). Such use, while neither requested by the sponsor nor endorsed by the Agency at the moment, should probably be investigated soon, before it becomes wide spread.

Patients to be treated with ramipril according the new indication should receive the optimal therapies for the underlying disease, including aspirin, beta-blockers and/or lipid lowering drugs. There is no evidence of interaction between ramipril and such agents in the HOPE study.

* As noted above, patients not receiving aspirin at baseline appeared to have a much greater effect, but ramipril remained beneficial for those who were so treated with aspirin

Secondary Endpoints

Statistically speaking, revascularization was the only secondary endpoint reduced significantly by ramipril (see Efficacy Results above on Page 5). There was no treatment difference in hospitalization for unstable angina and event rates of hospitalization for heart failure were probably too low to show an effect. As demonstrated by the sponsor's analyses, ramipril appeared to decrease cardiac arrest, heart failure and worsening angina (using check box on case report forms, not hospitalization, see Table on Page 5). Because these endpoints were not pre-specified in the protocol, the reviewers are reluctant to accept these findings as conclusive.

Nevertheless, it is difficult to believe that these events are totally unrelated to those of the primary endpoint and would not have similar treatment effects. On the other hands, these secondary endpoints, pre-specified or not, most likely represent various manifestations of the same disease spectrum. Therefore there is no need to describe in details the indirect benefit of ramipril treatment (including revascularization), which is reasonably implied by the main efficacy claim. The approved labeling should be silent in this respect.

Diabetes related Claims

As noted above, the reviewers are not convinced that ramipril has been shown to reduce new cases of diabetes mellitus in the main HOPE study. Again, this preventive claim is an isolated surprise and too important in public health to be approved with less data than meeting the usual statistical standards. Since patients as identified in HOPE will be treated with ramipril after approval of this efficacy supplement, however, it will be ethically difficult to initiate another parallel placebo controlled trial.

While there is no question that ramipril also improve the primary cardiovascular outcomes in patients with diabetes at baseline, it is much less clear whether the study drug also reduce the DM-specific microvascular complications. As described above, this part of HOPE data suffered from variable, not predefined endpoints and low individual event rates. One may argue that the truth about the claim of preventing overt nephropathy probably lies somewhere between a p value of 0.075 using protocol defined endpoints and a p of 0.045 for that modified in the published report. This renal claim is not inconsistent with the similar finding for captopril (although not in identical setting). On the other hand, results of the (retrospectively defined) composite endpoint for several microvascular events suggested that ramipril may be beneficial in reducing these complications in diabetic patients. The reviewers are leaning toward non-approval for this claim, but will not be surprised if the Advisory Committee recommend otherwise.

DRAFT LABELING

The draft labeling submitted by the sponsor will be further edited after the Advisory Committee meeting, a mark-up copy will be attached.

CONCLUSIONS

It is concluded that ramipril treatment at 10 mg once daily reduces risks of MI, stroke or cardiovascular death in patients with history of atherosclerotic vascular diseases and in patients with diabetes and at least one additional cardiovascular risk factor. Claim of indirect benefit, as suggested by the results of secondary endpoints, should not be described in the labeling. Decrease in new onset of diabetes and reduction in diabetes-specific microvascular complications has not been conclusively proven.

The risks of ramipril treatment in the new setting, most of which have been delineated and not more severe or frequent than previously known for the drug, are acceptable relative to the potential benefits.

It is recommended that ramipril be approved for the following new indication:

" Prevention of myocardial infarction, stroke, and death from cardiovascular causes:

/S/

/Shaw T. Chen, M.D., Ph.D.

cc:
ORIG: NDA- 19-901
HFD-110
HFD-110/Birdsong/Targum
HFD-710/Hung
HFD-110/SChen/04/30/2000

Date: April 26, 2000
From: Shari L. Targum, M.D., Medical Officer, HFD-110 ST 4/26/00
H.M. James Hung, Ph.D., Statistician, HFD-710 JH 4/26/00
Through: Director, Division of Cardiorenal Drug Products, HFD-110
To: Director, Office of Drug Evaluation I, HFD-100
Subject: Addendum to NDA 19-901, S-028

There are some minor discrepancies in some tables of our original review dated 04/03/00. In this addendum we made the changes to those tables. The following tables replace the corresponding tables in the original review. The changes do not affect the conclusions.

Table 2.1. Concomitant medications – 2 year visit

	Ramipril (N=4462)	Placebo (N=4472)
Beta blockers	1675	1804
Aspirin	3126	3198
Oral anticoagulants	245	229
Diuretics	738	854
Nitrates	1285	1364
Cholesterol-lowering drugs	1692	1712
Diltiazem/verapamil	1026	1066
Other calcium channel blockers	929	966
Estrogen	130	156
Folate	25	30
Vitamin C	254	242
Multivitamins	302	281
Nonsteroidal anti-inflammatory drugs	293	287
Alcohol	1584	1624
Beta carotene	43	36
If diabetic:* Insulin	557	588
Oral hypoglycemic agents	964	977

*For baseline diabetic treatment please see table 18.
This table was generated by the reviewer from the visit 7 and treatment group databases.

Table 4. Incidence of primary and related component outcomes

	Ramipril (N=4645)	Placebo (N=4652)	Hazard ratio (95% CI)	p-value
Cardiovascular death, MI, Stroke	651 (14.0%)	826 (17.8%)	0.78 (0.70, 0.86)	0.0001
Cardiovascular death	282 (6.1%)	377 (8.1%)	0.74 (0.64, 0.87)	0.0002
Myocardial Infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70, 0.90)	0.0003
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56, 0.84)	0.0002
Noncardiovascular death	200 (4.3%)	192 (4.1%)	1.03 (0.85, 1.26)	0.74
All-cause death	482 (10.4%)	569 (12.2%)	0.84 (0.75, 0.95)	0.005
All-cause death, MI, Stroke	822 (17.7%)	992 (21.3%)	0.81 (0.74, 0.89)	0.0001

Table 6. Myocardial Infarction by treatment

	Ramipril	Placebo
Symptoms (present)	383	472
Thrombolytic therapy	112	143
If unknown	14	24
ECG done	453	540
Anterior Q waves*	71	93
Anterolateral Q waves*	12	14
Lateral Q waves*	12	12
Inferior Q waves*	150	166
New Bundle Branch Block	41	56

This table was generated by checking boxes from the Myocardial Infarction Event Form provided by the sponsor.
*These categories are not mutually exclusive (e.g., patient ____ ____had both anterolateral and lateral Q waves on ECG).

Table 7. Incidence of secondary outcomes and other outcomes

	Ramipril (N=4645)	Placebo (N=4652)	Hazard ratio* (95% CI)	p-value*
Secondary outcomes				
Revascularization	743 (16.0%)	854 (18.4%)	0.86 (0.78, 0.94)	0.002
Hospitalization for unstable angina	554 (11.9%)	567 (12.2%)	0.97 (0.87, 1.09)	0.65
Hospitalization for heart failure	141 (3.0%)	161 (3.5%)	0.87 (0.69, 1.09)	0.22
Other outcomes (not prespecified)				
Cardiac arrest	37 (0.8%)	59 (1.3%)	0.62 (0.41, 0.94)	0.024
Heart failure**	417 (9.0%)	534 (11.5%)	0.77 (0.68, 0.87)	0.0001
Worsening angina$	1107 (23.8%)	1222 (26.3%)	0.88 (0.82, 0.96)	0.003
Hospitalization for unstable angina with ECG changes	175 (3.8%)	180 (3.9%)	0.97 (0.79, 1.19)	0.76

*All deaths are censored at the time of death

** This was a checkbox at every visit on the CRF

$ Worsening angina was defined a check box on the Unstable Angina Event Form next to the question "Was it increasing in severity or frequency?"

Table 9. Incidence of primary outcome by vitamin E stratification

	Ramipril n (%)	Placebo n (%)	Hazard ratio (95% CI)	p-value
Vitamin E group				
Cardiovascular death, MI, Stroke	338 (14.5%)	421 (18.2%)	0.79 (0.68, 0.91)	0.0009
All-cause death, MI, Stroke	424 (18.2%)	497 (21.5%)	0.83 (0.73, 0.95)	0.006
No Vitamin E group				
Cardiovascular death, MI, Stroke	313 (13.5%)	405 (17.3%)	0.76 (0.66, 0.89)	0.0003
All-cause death, MI, Stroke	398 (17.2%)	495 (21.1%)	0.79 (0.70, 0.91)	0.0006

Table 21. Incidence of cardiovascular outcomes

	Ramipril (N=1808)	Placebo (N=1769)	Hazard ratio* (95% CI)	nominal p-value*
Cardiovascular death, MI, Stroke	277 (15.3%)	351 (19.8%)	0.75 (0.64, 0.88)	0.0004
Cardiovascular death	112 (6.2%)	172 (9.7%)	0.63 (0.49, 0.79)	0.0001
Myocardial Infarction	185 (10.2%)	229 (12.9%)	0.78 (0.64, 0.94)	0.01
Stroke	76 (4.2%)	108 (6.1%)	0.67 (0.50, 0.90)	0.0074
All-cause death	196 (10.8%)	248 (14.0%)	0.76 (0.63, 0.92)	0.004
Revascularization	255 (14.1%)	292 (16.5%)	0.83 (0.70, 0.98)	0.031
Hospitalizations for unstable angina	213 (11.8%)	208 (11.8%)	0.99 (0.82, 1.20)	0.92
Hospitalizations for heart failure	81 (4.5%)	79 (4.5%)	0.99 (0.72, 1.34)	0.92

*All deaths are censored at the time of death

CC:
ORIG: NDA 19-901/S-028
HFD-110
HFD-110/BIRDSONG
HFD-110/Targum
HFD-110/Chen
HFD-710/Majoub
HFD-710/Hung
HFD-710/Chi

APR 17 2000

Date: April 17, 2000
From: Shari L. Targum, M.D., Medical Officer, HFD-110 ST 4/17/00
H.M. James Hung, Ph.D., Statistician, HFD-710 9H 4/17/00
Through: Director, Division of Cardiorenal Drug Products, HFD-110
To: Director, Office of Drug Evaluation I, HFD-100
Subject: Addendum to NDA 19-901, S-028

1. The following sentence and number replaces the "died during run-in period" number found on page 20 of the joint medical/statistical review dated 04/03/00.
Died during run-in period: 11 patients.

2. Tables 23 and 24 in the original joint medical/statistical review dated 04/03/00 are to be replaced by the following tables where the analyses take into consideration that the "time to outcome events" in a few patients were missing from the database and they were imputed with the "time to last follow-up visits" in the analyses. The changes in the analyses do not change our view regarding renal outcome endpoints and their composite endpoints.

Renal outcome endpoints

According to the protocol, overt nephropathy was defined as patient with ≥ 1+ proteinuria or urine albumin excretion > 200 microgram/min (or 300 mg/24 hours). In the reviewers' analysis, patients who had ≥ 1+ proteinuria reported during at least one of the yearly visits or urine albumin excretion > 200 microgram/min (or 300 mg/24 hours) reported in the 24 hour urine database were identified as those having overt nephropathy. The results are presented in the following table. The Lancet article presents three definitions of overt nephropathy, all of which are quite different from the protocol definition. The best p-value ($p = 0.045$) from the Lancet analyses for overt nephropathy was based on the definition of "develop an albumin/creatinine ratio of more than 36 mg/mmol if no 24 hour urine result available or have 24 hour protein excretion ≥ 500 mg or 24 hour urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours)". The result using this definition is also included in the table. There is no evidence that ramipril reduces the incidence of overt nephropathy, renal dialysis, need for laser therapy, microalbuminuria, or doubling creatinine at any post-randomization visit.

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ON ORIGINAL

Table 23R. Incidence of renal outcome endpoints

	Ramipril (N=1808)	Placebo (N=1769)	Hazard ratio* (95% CI)	nominal p-value*
Overt nephropathy[&]	249 (13.8%)	276 (15.6%)	0.86 (0.72, 1.02)	0.075
Overt nephropathy[$]	122 (6.8%)	110 (6.2%)	1.07 (0.83, 1.39)	0.60
Overt nephropathy[@]	122 (6.8%)	151 (8.5%)	0.78 (0.62, 0.99)	0.045
Penal dialysis[#]	10 (0.6%)	8 (0.5%)	1.20 (0.47, 3.05)	0.70
Laser therapy[#]	170 (9.4%)	186 (10.5%)	0.88 (0.72, 1.09)	0.24
Microalbuminuria[&]	431 (23.8%)	451 (25.5%)	0.94 (0.82, 1.07)	0.34
Doubling creatinine from baseline at any visit after randomization[!]	40 (2.2%)	28 (1.6%)	1.38 (0.85, 2.24)	0.19

[&] according to protocol definition: ≥ 1+ proteinuria reported at at least one of the yearly visits or urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) reported in urine 24 hours database

[$] ≥ 1+ proteinuria reported at at least one of the yearly visits or urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) reported in urine 24 hours database if urine 24 hrs measurements are available

[@] develop an albumin/creatinine ratio of more than 36 mg/mmol if no 24 hour urine result available or have 24 hour protein excretion ≥ 500 mg or 24 hour urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) [used in the Lancet article]

[#] from check box on case report form [also used in the Lancet article]

[&] definition provided by the HOPE group

[!] derived from the boxes on case report form

*All deaths are censored at the time of death

Composite renal endpoints

The Lancet article presents the results on incidence of composite endpoint of overt nephropathy, renal dialysis, or need for laser therapy. In the reviewers' analyses, several composite renal endpoints are examined as shown in the following table. Overt nephropathy was again analyzed using protocol definition and the Lancet definition that gives the best p-value. The results are quite different based on the definitions of overt nephropathy in term of nominal p-value and hazard ratio. In our view, there is not sufficient evidence to conclude that ramipril reduces the incidence of renal endpoints.

Table 24R. Incidence of composite renal endpoints

	Ramipril (N=1808)	Placebo (N=1769)	Hazard ratio* (95% CI)	nominal p-value*
Overt nephropathy^, laser therapy, renal dialysis	393 (21.7%)	416 (23.5%)	0.90 (0.78, 1.03)	0.13
Overt nephropathy$, laser therapy, renal dialysis	282 (15.6%)	281 (15.9%)	0.97 (0.82, 1.14)	0.70
Overt nephropathy@, laser therapy, renal dialysis	278 (15.4%)	314 (17.8%)	0.85 (0.72, 1.00)	0.05
Overt nephropathy^, laser therapy, renal dialysis, microalbuminuria	742 (41.0%)	782 (44.2%)	0.90 (0.81, 0.99)	0.034
Overt nephropathy$, laser therapy, renal dialysis, microalbuminuria	652 (36.1%)	672 (38.0%)	0.93 (0.84, 1.04)	0.18
Overt nephropathy@, laser therapy, renal dialysis, microalbuminuria	657 (36.3%)	717 (40.5%)	0.88 (0.79, 0.98)	0.016
Overt nephropathy^, laser therapy, renal dialysis, microalbuminuria, revascularization	891 (49.3%)	934 (52.8%)	0.89 (0.81, 0.98)	0.015
Overt nephropathy$, laser therapy, renal dialysis, microalbuminuria, revascularization	814 (45.0%)	846 (47.8%)	0.91 (0.83, 1.00)	0.055
Overt nephropathy@, laser therapy, renal dialysis, microalbuminuria, revascularization	814 (45.0%)	880 (49.8%)	0.87 (0.79, 0.96)	0.004

^ according to protocol definition: ≥ 1+ proteinuria reported at at least one of the yearly visits or urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) reported in urine 24 hours database

$ ≥ 1+ proteinuria reported at at least one of the yearly visits or urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) reported in urine 24 hours database if urine 24 hrs measurements are available

@ develop an albumin/creatinine ratio of more than 36 mg/mmol if no 24 hour urine result available or have 24 hour protein excretion ≥ 500 mg or 24 hour urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) [used in the Lancet article]

from check box on case report form [also used in the Lancet article]

& definition provided by the HOPE group

*All deaths are censored at the time of death

cc:
ORIG: NDA 19-901/S-028
HFD-110
HFD-110/Birdsong
HFD-110/SChen
HFD-110/Targum
HFD-710/Hung

APR - 3 2000

Combined Medical & Statistical Review
Heart Outcomes Prevention Evaluation (HOPE) Study

NDA #19-901, S-028

Division of Cardio-Renal Drugs, HFD-110

April 3, 2000

Overview

The sponsor has submitted a supplement for NDA 19-901, seeking approval for Altace® (ramipril) tablets as a treatment to reduce the risk of myocardial infarction, stroke, and cardiovascular mortality in "high risk" patients, defined as those with vascular or coronary disease, or diabetes with at least one other cardiovascular risk factor. This is a joint medical-statistical review of the submission.

Ramipril is currently approved for hypertension and post-myocardial infarction (MI) congestive heart failure (CHF); the latter approval was based on results from the Acute Infarction Ramipril Efficacy (AIRE) trial, a 2006 patient randomized, double-blind, placebo-controlled, parallel-group study in patients with CHF immediately post MI, which showed a reduction in the risk of death, progression of CHF, and CHF-related hospitalization.[1]

The sponsor now has presented the results (databases with an annotated case report form) of the HOPE (Heart Outcomes Prevention Evaluation) study, as well as manuscripts from The New England Journal of Medicine 342:145-153, 2000 (ramipril)[2], The New England Journal of Medicine 342: 154-160, 2000 (Vitamin E)[3] and The Lancet 355: 253-259, 2000 (diabetes substudy)[4] to support the new indication and usage. Efficacy data from substudies evaluating low-dose ramipril (2.5 mg per day), effects on echocardiograms in HOPE subjects (3 centers), and effects on carotid ultrasounds (SECURE study) were not provided in this submission and therefore are not included in this review. While Vitamin E was a randomized treatment in the factorial design of HOPE, its efficacy will not be discussed in great detail and no related indications are being sought at this time.

Draft labeling was received by the reviewers on February 22, 2000. Event forms for 50 patients were received on March 1, 2000. Ethnic/racial data were received on March 2, 2000. Also provided in the submission were protocols, protocol amendments, and minutes of the Data and Safety Monitoring Board. No Study Report was included in this submission.

The clinical data were reviewed jointly by Dr. Shari Targum (HOPE trial) and Dr. James Hung of Biometrics (statistical analysis). The secondary reviewer was Dr. Shaw Chen.

The Table of Contents can be found on the next page.

Table of Contents:

Background and History of Protocol Development:

Vascular disease resulting from atherosclerosis continues to be the number one cause of death in Western countries. Experimental evidence suggests that the development of atherosclerotic lesions is a complex chain of events involving oxidized low density liproproteins (LDL), endothelium, macrophages, vascular smooth muscle, platelets and circulating coagulation factors.

There has been experimental (in vitro and animal studies) and epidemiological evidence implicating the renin-angiotensin-aldosterone system in development of atherosclerosis. The hypothesis that angiotensin converting enzyme (ACE) inhibitors may be protective is supported by the several large trials of ACE inhibitors where there was a reduction in myocardial infarction (MI) compared to placebo. In the SOLVD trials, there were reductions in MI and unstable angina with enalapril use compared to placebo.[5] In the SAVE trial, there was a reduction in recurrent MI with captopril use compared to placebo.[6]

Since oxidized LDL is believed to be causally related to atherosclerosis, the question arose as to cardioprotective benefit with anti-oxidants. The question arose whether Vitamin E, as an anti-oxidant, could play a cardioprotective role.

A protocol (December 22, 1993), blank Case Report Form (CRF), and Ramipril Investigator's Brochure (revised October 1, 1990), were submitted to the Agency on December 30, 1993 as _____. In a January 31, 1994 letter to the sponsor (who, at that time, was the Principal Investigator), the Agency communicated the following concerns about the protocol:

1) Failure to exclude patients with prior congestive heart failure (CHF) or asymptomatic left ventricular dysfunction. The Agency recommended prospectively measuring ejection fraction in all patients, or measuring ejection fraction in a prospectively defined subgroup to see if there were differences in effect;
2) Definition of the primary endpoint to include "cause-specific mortality." The Agency strongly recommended that the primary combined endpoint be modified to "all cause mortality" instead;
3) Involvement of study physicians in the event report reviews and event adjudication. It was recommended that a panel of physicians blinded to therapy, and not involved in the conduct of the trial, review the events. It was also recommended that the Events Adjudication Committee review all cardiovascular deaths, rather than just those in which there is a discrepancy;
4) The Agency recommended that the decision to extend the follow-up period, if the total event rate is low, should be made by those independent of all aspects of the trial and blinded to the results. Those making this decision should only be informed of the total event rate, or the event rate in the placebo group only. Furthermore, this decision should be made at the time of the first or second interim analysis.
5) Inadequate definition of MI and inadequate MI documentation in the CRF;

6) The Agency recommended that the sponsor consider changing nephropathy/dialysis to a primary endpoint. The portion of the trial evaluating the progression of diabetic nephropathy was felt inadequate with regard to the determination of baseline measurements and documentation of events (i.e., proteinuria and dialysis). "Overt nephropathy" was inadequately defined. Also, baseline urine collection was inadequate for defining those with microalbuminuria. The Division recommended 24 hour urine collection either on all diabetics prior to the run-in, or at least in those with a positive morning urine.

7) Type of diabetes was not recorded on the CRF;

8) With the approval of captopril for diabetic nephropathy, it was recommended that this information be incorporated into the protocol and informed consent.

9) The protocol and consent form did not discuss precautions for patients on ramipril with hepatic insufficiency, elderly, requiring a diuretic, hypotension, history of angioedema, and on lithium;

10) The Agency recommended that concomitant medication, at least aspirin and beta blocker use, be recorded at all follow-up visits.

11) The design strategy could overestimate the effect of ramipril or vitamin E alone when synergism occurs;

12) If statistical analysis was not unequivocally reached on the primary endpoint, then analysis of the secondary endpoints will not be reliable enough to lead to definitive conclusions on the secondary endpoints;

13) The Agency requested the plan for interim analysis.

In a February 1, 1994 response, the sponsor agreed to prospectively study a 700 patient subgroup with 2D echocardiography, to determine the sample proportion with low ejection fraction. Patients with diabetic nephropathy would be excluded from randomization. Diabetics would be screened yearly for development of nephropathy. Those who developed diabetic nephropathy may be withdrawn from the study and offered open-label captopril or another ACE inhibitor, depending on their type of diabetes. Overt nephropathy remained a secondary endpoint and was defined, in that February 1, 1994 letter, as a 24 hour urine protein excretion of $\geq$ 500 mg, a 24 hour urine albumin excretion of $\geq$ 300 mg or a urinary albumin excretion rate of $\geq$ 200 micrograms per minute (in the protocol, the urinary albumin excretion rate is listed as > 200 micrograms per minute); this definition was not in the protocol amendments. In adjudicating events, the sponsor planned to have a random proportion of events independently checked by the Event Adjudication Committee (this was not in the protocol amendments). It was proposed that the Data and Safety Monitoring Board make the decision early in the process (e.g. before one-third of the events are in) whether to extend the study. Inclusion criteria for coronary artery bypass (CABG) and myocardial infarction (MI) were clarified and amended.

A summary of protocol amendments, dated March 21, 1994, was included in this submission. Many of the protocol amendments, such as additional eligibility definitions (for example, adding stress test results to define eligible patients), secondary endpoints, and safety monitoring, were added to a subsequent second version of the protocol, dated December 22, 1993 (while labeled "final version," this protocol is actually different from the other December 22, 1993 "final version" that the Agency received in December, 1993). The only change in definition of primary or secondary endpoints is the addition of Q wave/R wave criteria to the definition of a Q-wave MI . Changes to the older version of the protocol received in 1993 are—where applicable-- italicized below and include: changes in participant eligibility, data collection (in unusual circumstances medications could be mailed to patients), and safety monitoring. A "suggestion" for early termination of the trial was proposed in the protocol amendments but "formal stopping rules of a statistical sort" were subsequently rejected by the Data Safety and Monitoring Board.

The Claims:

In FDA form 356h, ,the sponsor proposed the following new indication for ramipril:

Financial Disclosure:

Financial disclosure statements were received on March 10, 2000. A completed FDA Form 3454 was received with box 2 checked, certifying that no investigators had a proprietary interest in the product, no compensation affected by study outcome, and no significant equity interest in the sponsor. The HOPE International Steering Committee, chaired by Dr. Salim Yusuf, administered and disbursed all funding for the HOPE trial. Funding sources for the study as well as the names and addresses of 905 investigators were provided. There appear to be no financial conflicts of interest.

The HOPE Protocol

Four different versions of the HOPE protocol, dated September 27, 1993, two versions dated December 22, 1993, and another version dated March 21, 1994, respectively, were submitted to the Agency. In addition, a summary of protocol amendments, dated 3/21/94, was submitted; these changes were then incorporated into the final version of the protocol. Since the study began in December, 1993, changes subsequent to the earlier second version of the HOPE protocol are underlined and italicized below.

Title of Study: Heart Outcomes Prevention Evaluation

Objectives:

There were two primary objectives:

1. To evaluate if ramipril use reduces the composite endpoint of myocardial infarction, stroke and cardiovascular death in patients at risk for cardiovascular events.
2. To evaluate if Vitamin E use reduces the composite endpoint of myocardial infarction, stroke and cardiovascular death in patients at risk for cardiovascular events.

The primary endpoint was, therefore, the occurrence of myocardial infarction, stroke, or cardiovascular death.

Secondary endpoints:

Secondary endpoints were: hospitalization for congestive heart failure, acute ischemic cardiac syndromes (MI, unstable angina or severe angina requiring emergency coronary artery bypass surgery or angioplasty), all cardiovascular revascularization procedures, cardiovascular mortality, total mortality, overt nephropathy or dialysis among diabetics, cancer by site and morphology.

Study Design:

This was a randomized, placebo-controlled, double-blind trial, utilizing a 2 x 2 factorial design (see below), with a 3 week run-in period followed by 48 months of treatment.

Number of Patients to be Recruited:

8,000 total (see Sample Size calculation), to be recruited over a one year period, including about 4,000-5,000 cardiac, 1,000 peripheral vascular, and 3,000-4,000 high risk diabetics (including 1,000-2,000 with cardiac disease).

Investigators and Sites of Investigation:

The Principal Investigator was Dr. Salim Yusuf, McMaster University, Toronto, Canada.
The protocol specified 200 sites, distributed as 100-120 sites in Canada, 20-30 in the United States, 50 in Europe, and 30 in South America. The NEJM manuscript[2] noted 129 centers in Canada, 27 centers in the United States, 76 centers in 14 western European countries, 30 centers in Argentina and Brazil, and 5 centers in Mexico.

Patient Population:

Males and females aged 55 and over at high risk of developing a major cardiovascular event.

Inclusion Criteria:

1. Coronary disease:

- Previous MI
- *Stable or* unstable angina with documented multivessel coronary disease, *defined as >50% stenosis in at least two major coronary arteries or positive stress (ST depression > 2 mm) or positive thallium*
- Multivessel PTCA

(patients can be entered into run-in phase one week after these events but should only be randomized one month after these events).

- Multivessel CABG (more than 4 years ago *or with angina*)
- Multivessel coronary disease (*defined as above*) on angiography.

2. Peripheral vascular disease:
- Previous limb bypass surgery or percutaneous transluminal angioplasty
- Previous limb *or foot* amputation
- History of intermittent claudication with ankle/arm blood pressure ratio of 0.80 or lower *in at least one side*
- *Significant stenosis (>50%) documented by angiography*

3. Previous nondebilitating stroke: (more than one month ago)

4. Diabetes (insulin-dependent or noninsulin-dependent) with one of the following cardiac risk factors:
- Hypertension (BP > 160 mmHg systolic or > 90 mmHg diastolic or on treatment)
- Total cholesterol > 5.2 mmol/L (>200 mg/dl)
- HDL cholesterol < 0.9 mmol/l (35 mg/dl)
- Current cigarette smoking
- Known microalbuminuria *or any evidence of previous vascular disease*

Exclusion Criteria:
- Use of ACE inhibitors or Vitamin E with an inability to discontinue these medications;
- Known hypersensitivity to ACE inhibitors or Vitamin E.
- Ejection fraction < 40% (only if known).
- Hemodynamically significant primary valvular or outflow tract obstruction.
- Constrictive Pericarditis.
- Complex congenital heart disease.
- Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias.
- Planned cardiac surgery or angioplasty within 3 months (patients may be reconsidered after the procedure).
- Uncontrolled hypertension.
- Cor pulmonale.
- Heart transplant recipient.
- Significant renal disease, defined as
  1. Renal artery stenosis
  2. Creatinine clearance < 0.6 ml/second or serum creatinine ≥ 200 Meq/L (≥ 2.26 mg/dl)
  3. Overt nephropathy: ≥ 1 plus proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hours)
  4. Hyperkalemia; K > 5.5 mEq/L.
- Any other major noncardiac illness expected to reduce life expectancy or interfere with study participation.
- Simultaneously taking another experimental drug.
- Previously randomized to HOPE.

Withdrawal Criteria:

- Congestive heart failure: Patients who developed congestive heart failure were to be discontinued from ramipril and given open-label ACE inhibitors.
- Cardiac Transplantation.
- Severe adverse experiences: Withdrawal was at the discretion of the treating physician.
- Overt nephropathy: Development of overt nephropathy during the trial was not strictly a criteria for withdrawal, but was left up to the "judgement of the investigator." All patients withdrawn from study medication would remain in the study and were to be analyzed in their originally allocated group.

In the management of MI, unstable angina, hospitalization for other medical illnesses or for surgery, CABG, percutaneous transluminal coronary angioplasty (PTCA), hyperkalemia, or uncontrolled hypertension, patients were encouraged to either continue medication or temporarily hold and restart medication as soon as feasible. In the case of azotemia, it was recommended to continue ramipril at a lower dose. None of these conditions were considered to be criteria for withdrawal from study medication.

Randomization:

Randomization was provided by the Canadian Cardiovascular Collaboration Program Office (C3PO).

Dosage/Administration:

Patients were randomized to ramipril (2.5 mg once daily (QD) for one week, then 5 mg QD for 3 weeks, then 10 mg QD) or placebo AND Vitamin E 400 IU QD or placebo. The time of administration (i.e., day or evening) was not specified in the protocol or case report form.

Duration of Study:

The protocol specified a follow-up schedule out to 48 months. Patients were to be followed for an average of 3.5 years. The study was to end after the last patient was followed for at least 3 years. According to the C3PO the study was to have ended in November 1998. The study was extended to November, 1999 to allow for late-appearing Vitamin E effects. In March, 1999, the Data and Safety Monitoring Board, which had access to the unblinded data, recommended stopping the ramipril portion of the study for efficacy reasons.

Study Plan:

Eligible patients entered a 3 week run-in period where they received 2.5 mg ramipril for 7-10 days followed by placebo ramipril for 10-14 days. Urine dipstick for proteinuria was to be done on the first visit, and serum creatinine and potassium were to be performed between days 7 and 10 of the run-in period (on active ramipril). In diabetics, a glycosylated hemoglobin (Hb A1c) would be done. Patients were eligible to enter the double-blind phase if they were compliant (>80 %), had no contraindications to therapy, met eligibility requirements, did not have gross elevations in potassium or creatinine, $\geq$ 1+ proteinuria or severe adverse effects. Patients were then randomized to the following groups:

Ramipril + Vitamin E (2,000)	Placebo Ramipril + Vitamin E (2,000)
Rampril + Placebo Vitamin E (2,000)	Placebo Ramipril + Placebo Vitamin E (2,000)

During the double-blind phase, follow-up visits occurred at 1 and 6 months, then every 6 months up to 48 months post-randomization. Patients without diabetes would have a serum creatinine and potassium at the 1 month visit only. Diabetics would have yearly serum creatinine and glycosylated hemoglobin.

Schedule and Methods of Assessment:

Run-In Visit (visit 1) (-3 weeks)	Demographics, Eligibility Determination If diabetic, urine dipstick for proteinuria
Prior to randomization (visit 2) (week 0)	Mortality, hospitalization, serious, related adverse event Medical History, including risk factors, medication use Physical Exam, including heart rate, blood pressure, ankle blood pressure, height, weight Waist and Hip Circumference 12-lead ECG (within last 12 months if no new CV event) Compliance to run-in medication Blood samples for creatinine, potassium and (if diabetic) glycosylated Hb Urine sample for microalbuminuria (central lab) Blood sample, 8 hour fasting, selected sites (central lab)
Follow-Up (visit 3) (1 month)	Mortality Compliance with study medication Clinical events recorded Heart rate, arm blood pressure, ankle blood pressure Creatinine and potassium (local lab)
At 6 months (visit 4)	Mortality, Clinical events and serious adverse events, compliance
At 1 year (visit 5)	Mortality, Clinical events and serious adverse events Compliance with study medication If diabetic, record serum creatinine, glycosylated Hb(local lab) If diabetic, urine dipstick for proteinuria (urine sample to be sent to HOPE central lab)

Schedule and Methods of Assessment (continued):

At 1.5 years (visit 6)	Mortality, Clinical events and serious adverse events Compliance with study medication
At 2 years (visit 7)	Mortality, Clinical events and serious adverse events Compliance with study medication Medication history If diabetic, record serum creatinine, glycosylated Hb (local lab) and urine dipstick (urine sample to be sent to HOPE central lab) Heart rate, arm blood pressure, ankle blood pressure 12-lead ECG
At 2.5 years (visit 8)	Mortality, Clinical events and serious adverse events Compliance with study medication
At 3 years (visit 9), 4 years (visit 11), 5 years (visit 13)	Mortality, Clinical events and serious adverse events Compliance with study medication If diabetic, record serum creatinine and glycosylated Hb from local lab If diabetic, urine dipstick for proteinuria (need not be sent centrally)
At 3.5 years (visit 10), 4.5 years (visit 12), and 5.5 years (visit 14)	Mortality, Clinical events and serious adverse events Compliance with study medication
At penultimate visit	Medication history, ECG, urine sample (central lab), creatinine and glycosylated Hb from local lab
Final visit	Heart rate, arm and ankle blood pressures, height/weight

Definitions of Efficacy Endpoints

Primary Endpoints:

Measures of efficacy were described as "primary endpoints." The primary endpoint was defined in the protocol as the first occurrence of either nonfatal MI, nonfatal stroke, or death from a cardiovascular cause.*

1. Nonfatal MI:

(a) Q wave MI: New significant Q waves (≥ *0.04 seconds duration or 3-4 mm depth and loss in height of ensuing R wave)* in at least two leads on the standard 12 lead ECG and at least one of :

* see Event Adjudication Committee, next page, for which events were adjudicated.

- typical associated symptoms (e.g. chest pain) and/or
- significant enzyme elevation—any one of the following:
  --CPK-MB above the upper limit of normal within 36 hours of onset of symptoms plus total CPK at least twice the upper limit of normal
  --SGOT, LDH, or other cardiac enzymes at least twice the upper limit of normal for the laboratory that performed the test with a characteristic pattern.

(b) MI without ECG changes or minimal ECG changes: patients with characteristic symptoms plus characteristic elevation of cardiac enzymes. In such cases ECG changes may be minimal, transient or non-diagnostic.

(c) Non Q wave MI: New, persistent ST or T wave changes on the ECG with significant enzyme elevation and/or symptoms of chest pain.

(d) Silent Q wave MI: New Q waves in at least 2 adjacent leads (without symptoms or enzyme elevation).

The diagnosis of MI was made at the site.

2. Stroke: Neurologic deficits persisting for more than 24 hours. Strokes were further classified, based on clinical symptoms, autopsy and/or CT/MRI as:

a) Definite or probable ischemic stroke
b) Definite or probable hemorrhagic stroke
c) Definite stroke, type uncertain.

3. Cardiovascular death: Any deaths due to MI, stroke, pulmonary emboli, arrhythmia or other cardiovascular events (i.e. ruptured aorta). This includes sudden death without any other documented cause.

Secondary Endpoints:

1) Acute ischemic cardiac syndromes: MI, plus unstable angina or severe angina requiring emergency CABG or PTCA (i.e., within 7 days of symptom onset).
2) All cardiovascular revascularization procedures to include CABG surgery, coronary PTCA, carotid endarterectomy (for stenosis of carotid luminal wall, transient ischemic attacks or stroke), peripheral cardiovascular surgery or angioplasty (for limb ischemia), or limb amputation.
3) Cardiovascular mortality.(Although listed this way, this endpoint is the same as "cardiovascular death", counted as an individual component (per C3PO) rather than a composite.)
4) Total mortality.
5) Development of overt nephropathy or dialysis among diabetics.
6) Hospitalization for congestive heart failure.
7) Cancer by site and morphology.

Event Adjudication:

According to the protocol, the Event Adjudication Committee were to review only those major events (MI, stroke, CV death) where there was a discrepancy between the hospital record or death certificate and the case report form/event form. A C3PO physician was to review all discharge summaries and event forms for consistency.

According to additional information supplied by the C3PO (not in the protocol or amendments), all primary and secondary endpoints (event reports and supporting documentation) were reviewed by a member of the Event Adjudication Committee. If there was disagreement between the committee member and investigator, the event was sent to the committee chair (Dr. Dagenais) for final decision. Only certain committee members were allowed to adjudicate deaths. In addition, a blinded committee member reviewed 10% of those events confirmed by an adjudicator.

According to the C3PO, the primary endpoint was the composite of the "first event." A hypothetical patient who sequentially developed an MI, then a stroke, and then died of a pulmonary embolus would have reached the primary endpoint with the MI (the first event).

Case Report Forms

The blank Case Report Forms, as provided in the submission are, in general, adequately designed for collection of pertinent data. For diabetics, age of diabetes onset and medications (but not dosages) were elicited. Specific concurrent medications were elicited at the randomization visit, at the 2 year visit, and at the penultimate visit. There were specific Event Forms for: hospitalization, MI, stroke, death, unstable angina and serious adverse experiences.

Organization and Monitoring of the HOPE Study:

Sites/Investigators: Sites to consist of universities, community hospitals, and private clinics. Investigators to recruit and follow patients, and meet annually to discuss overall trial conduct and hold educational forum.

Regional Coordinators: Regional follow-up, organize screening and recruitment

Canadian Cardiovascular Collaboration Project Office (C3PO)—day to day conduct of the trial

International Steering Committee: Includes chairs and regional coordinators. Disbursed funding (see Financial Disclosure). Chaired by Principal Investigator, Dr. Yusuf

Events Adjudication Committee: Review and classify components of the primary composite endpoint where questions or discrepancies occurred.

Data Safety & Monitoring Board: Independent scientific review of protocol, recommend changes, early termination of study, ensure event rates are reasonable.

The C3PO was the most important group in organizing and managing the trial, and, together with the International Steering Committee and the Events Adjudication Committee, had overall responsibility for the trial. As mentioned above, the International Steering Committee disbursed funding.

Several members of the International Steering Committee were also members of the Events Adjudication Committee (G. Dagenais, E. Lonn, M. Arnold, H. Gerstein, and A. Avezum); E. Lonn was also a Coordinator of the study.

The Data Safety and Monitoring Board (DSMB), the only group that had access to unblinded data, did not include investigators or coordinators as members. According to DSMB minutes, the Principal Investigator (Dr. Yusuf) was not in attendance when unblinded data were shown; it was agreed –per DSMB minutes—that the Principal Investigator would remain blinded to efficacy data until about six months prior to the expected end of the study.

Study design:
As in the HOPE trial, diabetic patients will take ramipril or matching placebo AND Vitamin E or matching placebo in a 2 x 2 factorial design (see HOPE Study design). They will be followed every 6 months up to 48 months.

Patient population:
This patient population represents the same diabetic population that was recruited as part of the HOPE trial, namely diabetics with at least one other of four cardiac risk factors (See above: hypertension, hyperlipidemia, active smoking, or known microalbuminuria. Other risk factors such as family history, obesity, etc. were not part of the eligibility criteria). This population included those with non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM), and those with and without coronary disease.

Exclusion criteria:
These would be the same exclusion criteria as in the main HOPE trial, and include absolute indications or contraindications for the use of ACE inhibitor or Vitamin E, or medical problems that would either interfere with participation in the trial or lead to the inability to complete the trial.

Study plan:
This would entail the same dosage/administration and schedule of events as in the main trial. Additional information collected during the run-in phase and at each year visit would include: serum creatinine and glycosylated Hgb (Hgb A1c), as well as a urine sample for microalbuminuria. Also collected was reporting of laser surgery for retinopathy.

Summary of Reviewer Comments on Protocol:

- The eligibility criteria broadly defined those "at risk" for vascular events; these criteria included post MI or post PTCA patients regardless of stress test results. In this regard, a hypothetical post MI patient (without stress test or coronary angiogram results) would have been included whereas a patient with angina and single vessel disease would have been excluded.
- The primary endpoint in the main study was a composite, including "cause-specific" (i.e., cardiovascular causes) mortality. All-cause mortality was defined as a secondary endpoint.
- According to the protocol, major events (the components of the primary composite endpoint) were adjudicated centrally only in the case of questionable events or discrepancies.

- The diagnosis and type of diabetes was not predefined. Age of onset of diabetes, but not type (Insulin-dependent/Noninsulin-dependent diabetes) was specified on the Case Report Form. According to the February 1, 1994 letter from the sponsor to the Agency, the two groups were distinguished by age of onset of diabetes. However, this distinction was not prospectively defined, nor can any definition be found in the protocol or protocol amendments. C peptide levels, reflecting endogenous insulin production, were not drawn. According to the Lancet manuscript[4], the two groups were distinguished by age of diabetes onset (age 30 was used as a cutoff) or medication use (i.e., not on insulin). The age definition might misclassify some patients.
- Deaths from pulmonary emboli were included in cardiovascular mortality. Pulmonary emboli can occur in the absence of atherosclerotic disease.
- In the protocol, overt nephropathy was prespecified as a "secondary research question." In the manuscript, overt nephropathy was a "main outcome in a substudy."
- Differing definitions of overt nephropathy:
  - According to the protocol, overt nephropathy (see Exclusion) was defined as $\geq$ 1+ proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hours).
  - According to the Principal Investigator (letter to the Agency, February 1, 1994), "Patients with an albumin creatinine ratio of 30 at the one year follow-up and at the end of the study will be considered to have possible overt diabetic nephropathy. This information will be communicated to the investigators who will be asked to confirm the presence of overt diabetic nephropathy."
  - According to the published diabetes substudy design,[7] the albumin-to-creatinine ratio and urine protein dipstick were to be used as screening tests for overt nephropathy and the diagnosis was to be confirmed with 24 hour or timed urine albumin or protein.
  - According to the Lancet manuscript,[4] patients with a first morning urinary albumin/creatinine ratio of 36 mg/mmol or higher were asked to give a 24 hour urine sample which was assayed in a local laboratory. Overt nephropathy was defined as 24-hour urine albumin of 300 mg or more per day, 24-hour urine total protein excretion of 500 mg or more per day, or if the albumin/creatinine ratio was higher than 36 mg/mmol and no 24-hour urine result was available (central assessment was done for 24 hour urines in cases of overt nephropathy). This definition was not in the protocol or amendments.
- Microalbuminuria was not predefined in the protocol or protocol amendments. In the Lancet manuscript[4] microalbuminuria was defined as an albumin/creatinine ratio of $\geq$ 2 mg/mmol and the reader is referred to another journal article describing the HOPE trial methods.[7] In this reference, microalbuminuria is defined as a urine albumin excretion rate of 20-200 µg/min.
- In diabetics, glucose control was a "secondary question" but analysis of this parameter was not further predefined in the protocol or amendments.
- In the protocol, the only prespecified "composite endpoint" was that of the primary endpoint. A "combined microvascular outcome" of overt nephropathy, dialysis, or laser therapy, as published in the manuscript,[4] was not prespecified.
- In the protocol, deterioration in renal function was mentioned as a "secondary question" but was not further defined.

- Congestive heart failure was not a predefined outcome and was not further defined in the protocol or amendments. There was a Congestive Heart Failure form (plate 052), with information on diagnosis and treatment, which was not included in this submission and not previously submitted to the Agency. Hospitalization for congestive heart failure, but not congestive heart failure itself, was a prespecified secondary endpoint.
- Information regarding laser therapy in diabetics was collected by patient history and checking a box on the CRF next to the question, "has the patient required laser therapy for diabetic retinopathy since the last study visit." No retinal photos or angiograms were specifically elicited either at baseline or during the study. A baseline imbalance in retinopathy between ramipril and placebo cannot be excluded in this study. Changes from baseline in retinopathy, or recommendations for laser therapy, were not assessed. Since this is a self-reported measure, there is the error introduced by patient interpretation and understanding of the question and laser procedure.
- Management of adverse events were at the discretion of the patient's physician. "When in doubt," the treating physician was encouraged to discuss an individual patient's management with the C3PO. A potential bias resulting from advice provided by the C3PO cannot be excluded.

Termination of HOPE study

As mentioned previously, the statistical monitoring boundary indicating that ramipril had a beneficial effect was a difference in the primary endpoint of 4 standard deviations between groups during the first half of the study and of 3 standard deviations during the second half. According to the New England Journal of Medicine article, on March 22, 1999, the Data Safety Monitoring Board (DSMB) recommended termination of the HOPE study because of the clear evidence of a beneficial effect of ramipril (consistent crossing of the monitoring boundaries in two consecutive reviews). At that time, the data showed a 20 percent reduction in the relative risk of the primary endpoint (95% CI of 12% to 28 % reduction; z statistic = -4.5, $p < 0.001$). The results of the study were disclosed to the investigators at two meetings on April 17 and April 24, 1999. The cutoff date for all events included in the main analysis was set for April 15, 1999, and the final visits were scheduled to be completed by June 30, 1999.

Comments: The DSMB meeting minutes of March 22, 1999 reported that they concluded that the data were extremely convincing for the efficacy of ramipril for both primary and secondary outcomes. There was no meeting minutes reporting that the data had crossed the monitoring boundaries in two consecutive reviews.

Results:

Patient Description:

Patient Disposition:
I. the database provided, 10, 585 patients entered the run-in phase; 1044 patients were excluded from randomization.* Reasons for rejection were:

1044 patients rejected from randomization: †
Refused/withdrew consent/administrative: 338
Did not meet eligibility criteria**: 345

Patients who did not meet eligibility criteria:

Age < 55	83
CHF/EF < 40%	16
>1+ proteinuria	11
Insufficient coronary artery disease	18
CABG < 4 years without symptoms	17
Increased potassium/creatinine during run-in	58
On Vitamin E/ACE inhibitor	23
noncompliant during run-in	108
other/unspecified**	11

** One patient [redacted] was not randomized due to "revised entry criteria."

Adverse events during run-in: 259
Died during run-in period: 10
Other medical illness/clinically unstable: 74
No show/lost to followup: 18

Of the adverse events leading to withdrawal during run-in, the most commonly reported were:

Unspecified 52
Cough 39
Dizziness 34
Nausea 27
Headache 21
Facial swelling/angioedema was reported in 3 patients.

* According to the NEJM manuscript,[2] 10, 576 eligible patients entered into the run-in phase. Of these, 1035 patients were excluded from randomization because of noncompliance, side effects, abnormal serum creatinine or potassium levels, or withdrawal of consent.

† These data were generated by the reviewer from the visit 2 (randomization visit) database (spreadsheet) supplied by the sponsor. Eligibility was determined from a checkbox, labeled yes/no. Under the reasons patients were excluded from randomization, several entries were in languages other than English or not specified. "Didn't feel well" without clarification was classified as adverse event, unspecified.

Of the remaining 9541 patients, 4645 were randomly assigned to ramipril 10 mg per day, and 4652 were randomly assigned to matching placebo; 244 patients were randomly assigned to receive ramipril 2.5 mg per day—these low-dose patients were not included in the efficacy analysis in this submission.
In the database provided there were 8514 patients who underwent a final visit; 8 patients were unaccounted for/lost to follow-up: 5 in the placebo group, and 3 patients in the ramipril group.*

Demographics and Baseline Characteristics:

The ramipril group and the placebo group appeared to be well balanced at baseline (Table 1).

Table 1. Demographics and baseline characteristics

	Ramipril (N=4645)	Placebo (N=4652)
Gender		
Male	72.5%	74.2%
Female	27.5%	25.8%
Ethnic group		
Caucasian	89.7%	89.7%
Hispanics	5.7%	5.8%
Asian	1.7%	1.6%
Blacks	1.6%	1.4%
Native	0.3%	0.3%
Others	0.9%	0.9%
Age (in yr)	66±7	66±7
SBP/DBP (in mm Hg)	139±20/79±11	139±20/79±11
Heart rate (in bpm)	69±11	69±11
Body mass index	28±4	28±4
History of cardiovascular disease	86.8%	88.8%
History of coronary artery disease	79.5%	81.4%
Myocardial infarction	51.9%	53.4%
Within ≤ 1 year	9.7%	9.6%
Within > 1 year	42.2%	43.8%
Stable angina	54.8%	56.3%
Unstable angina	25.4%	25.5%
CABG	25.7%	25.9%
PTCA	18.4%	17.3%
Stroke or transient ischemic attacks	10.8%	11.0%
Peripheral vascular disease	40.0%	42.3%
Hypertension	47.6%	46.1%

* According to the C3PO there were 6 patients lost to follow-up after randomization: 4 in the placebo group and 2 in the ramipril group.

Table 1. Demographics and baseline characteristics (continued)

	Ramipril (N=4645)	Placebo (N=4652)
Documented elevated total cholesterol level	65.4%	66.4%
Documented low HDL cholesterol level	18.1%	18.9%
Current cigarette smoking	13.9%	14.5%
Medications		
Beta blockers	39.2%	39.8%
Aspirin or antiplatelet agents	75.3%	76.9%
Lipid-lowering agents	28.4%	28.8%
Diuretics	15.3%	15.2%
Calcium-channel blockers	46.3%	47.9%
Left ventricular hypertrophy on electrocardiography	8.2%	8.7%
Diabetes	38.9%	38.0%
Microalbuminuria	20.5%	21.6%

Protocol Violations/Deviations:
Protocol violations/deviations were not mentioned in the protocol or any of the manuscripts.

According to the DSMB minutes, "procedural deficiencies" were noted in 2 centers, and "protocol violations" were noted in center 6. However, according to the C3PO, no centers were excluded because of protocol violations. Also, excluding center 6 did not affect the analysis and results, according to the reviewers' analysis.

Six randomized patients, 4 to placebo ramipril and 2 to ramipril, were noncompliant during the run-in period and therefore did not meet that eligibility criterion. *
One patient randomized to the ramipril treatment group, had a rise in potassium during the run-in period and was therefore ineligible on that basis.

Concomitant Therapies:
Information concerning selected concomitant therapies was collected at randomization, at the 2 year visit, and at the penultimate visit. As noted above, the two groups were evenly distributed regarding the use of beta blockers, aspirin/antiplatelet agents, lipid-lowering agents, diuretics, and calcium channel blockers.

Eight patients (3 in the placebo ramipril and 5 in the active ramipril group) had no history of diabetes but were on oral hypoglycemic agents.

* Data regarding patient eligibility were generated from analysis of the visit 2 database provided by the sponsor.

One patient [redacted] on placebo ramipril had no history of diabetes but was on insulin.
Two patients [redacted] on active ramipril had no history of diabetes but were on insulin.*

The above table lists concomitant medications at randomization. Other concomitant medications for ramipril and placebo at randomization included:

Table 2. Other concomitant medications—baseline

Medication	Ramipril (N=4645) n	Placebo (N=4652) n
Estrogen	115	151
Vitamin C	280	257
Beta carotene	61	62
Multivitamins	331	323
Alcohol	1842	1870

This table was generated by the reviewer from the visit 2 and treatment group databases.

At the two year visit, concomitant medications were as follows:

Table 2.1. concomitant medications—2 year visit

Medication	Ramipril (N=4645) n	Placebo (N=4652) n
Beta blockers	1733	1731
Aspirin	3151	3171
Oral anticoagulants	252	222
Diurctics	833	757
Nitrates	1299	1362
Cholesterol-lowering drugs	1704	1716
Diltiazem/verapamil	1033	1075
Other calcium channel blockers	988	895
Estrogen	144	144
Folate	31	25
Vitamin C	267	228
Multivitamins	304	289
Nonsteroidal anti-inflammatory drugs	278	302
Alcohol	1644	1560
Beta carotene	40	38
If diabetic:*		
Insulin	584	556
Oral hypoglycemic agents	979	959

*For baseline diabetic treatment please see table 18.
This table was generated by the reviewer from the visit 5 and treatment group databases.

* These data were generated from analysis of the visit 2 database provided by the sponsor.

At the penultimate visit, concomitant medications were as follows:

Table 2.2. Concomitant medications—penultimate visit

Medication	Ramipril (N=4099) n	Placebo (N=4047) n
Beta blockers	1565	1764
Aspirin	2807	2863
Antiplatelet agents	256	277
Oral anticoagulants	294	286
Diuretics	816	942
Nitrates	1100	1184
Cholesterol lowering drugs	2048	2022
Diltiazem/verapamil	806	808
Other calcium channel blockers	894	928
Estrogen replacement	100	132
Folate	90	102
Vitamin C	257	242
Beta Carotene	52	32
Insulin	614	591
Oral hypoglycemic agents	916	950
Nonsteroidal anti-inflammatory agents	253	237
Alcohol	1416	1401

This table was generated by the reviewer from the penultimate visit and treatment group databases.

Compliance:

Compliance was defined on the CRF as the patient taking at least 75% of study drug. The following table was generated from the visit and treatment group databases.

Table 3. Compliance

	1 year (visit 5)	2 year (visit 7)	3 year (visit 9)	4 year (visit 11)	Final visit
Ramipril group					
N	4580	4645	4364	3957	4188
Compliance > 75%	3788 (82.7%)	3580 (77.1%)	3270 (74.9%)	2848 (72.0%)	2870 (68.5%)
On 10 mg ramipril	3766 (82.2%)*	3488 (75.1%)	3103 (71.1%)	2705 (68.4%)	2705 (65.0%)
Ramipril stopped	665 (14.5%)	756 (16.3%)	996 (22.8%)	1040 (26.3%)	1235 (29.5%)
Ramipril dose changed**	149	N/A	N/A	N/A	N/A
Using nonstudy ACE inhibitor	101 (2.2%)	241 (5.2%)	259 (5.9%)	307 (7.8%)	401 (9.6%)
Using A2 antagonist	N/A	28 (0.6%)	36 (0.8%)	59 (1.5%)	68 (1.6%)
Placebo group					
N	4578	4652	4331	3897	4104
Using nonstudy ACE inhibitor	153 (33.4%)	217 (4.7%)	348 (8.0%)	418 (10.7%)	504 (12.3%)
Using A2 antagonist	N/A	22 (0.5%)	48 (1.1%)	58 (1.5%)	79 (1.9%)

* no separate entry. Number derived from: [total N- (n with dose change + n where ramipril stopped)] divided by total N. That result was multiplied by 100 to arrive at a percentage.
**This check box was only present at the 1 year visit.

For drug discontinuation and reasons for stopping please see Safety Data.

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Efficacy:

Primary clinical outcomes

The primary efficacy endpoint is the composite endpoint of cardiovascular death, myocardial infarction and stroke. Table 4 summarizes the comparisons of the two treatment groups on the primary clinical outcomes. Ramipril gave a statistically significant reduction in the incidence of cardiovascular death, MI and stroke and the incidence of all-cause death, MI and stroke. The effect of ramipril on each component event is consistent with that on the composite endpoint.

In 106 deaths, there were differences between the database report and the Events Adjudication Committee (e. g. the database reported a death as "MI" where the Event Adjudication Committee reported the same death as "non-cardiovascular" or the event was classified as "non-cardiovascular" but the Event Adjudication Committee reported the death as "cardiovascular"). The reviewer's analysis of the composite endpoint using the primary cause of death as classification criterion give the results almost identical to that of the composite endpoint using the adjudicated events.

Table 4. Incidence of primary and related component outcomes

	Ramipril (N=4645)	Placebo (N=4652)	Hazard ratio (95% CI)	p-value
Cardiovascular death, MI, Stroke	651 (14.0%)	826 (17.8%)	0.78 (0.70, 0.86)	0.0001
Cardiovascular death	282 (6.1%)	377 (8.1%)	0.74 (0.70, 0.90)	0.0002
Myocardial Infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70, 0.90)	0.0003
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56, 0.84)	0.0002
Noncardiovascular death	200 (4.3%)	192 (4.1%)	1.03 (0.85, 1.26)	0.74
All-cause death	482 (10.4%)	569 (12.2%)	0.84 (0.75, 0.95)	0.005
All-cause death, MI, Stroke	822 (17.7%)	992 (21.3%)	0.81 (0.74, 0.89)	0.0001

Mortality data:
The next table provides a breakdown of the primary cause of death, as classified in the database.

Table 5. All cause deaths: Primary cause of death

Event	Ramipril n	Placebo n
MI	84	111
Stroke	33	49
Ventricular tachyarrhythmia	17	24
Other sudden cardiac death	68	88
Worsening CHF	26	34
Pulmonary embolus	6	6
Other embolism	–	1

Table 5. Primary cause of death (continued)

	Ramipril n	Placebo n
Other cardiovascular	52	59 (+2)*
Amputation-related	2	1
Ketoacidosis	–	?
Nephropathy/Renal failure	1	2
Cancer	112	108
Other non-CV	81	82
Totals	482	569

This table was generated from the death and treatment databases.
*Two patients in the placebo group [redacted] did not have listed more specific primary causes of death. These patients were coded as "cardiovascular deaths" and are, therefore, entered into the "other cardiovascular" category.

Myocardial Infarction:

The following table lists data obtained from the MI database, obtained from the MI event sheets (unadjudicated). Note that these numbers represent numbers of events, not numbers of patients.

Table 6. Myocardial Infarction by treatment

	Ramipril	Placebo
Symptoms (present)	383	472
Thrombolytic therapy	112	143
If unknown	14	24
ECG done	453	540
Anterior Q waves*	83	114
Anterolateral Q waves*	12	14
Lateral Q waves*	10	14
Inferior Q waves*	11	12
New Bundle Branch Block	21	37

This table was generated from the Myocardial Infarction Event database provided by the sponsor.
*These categories are not mutually exclusive (e.g., patient [redacted] had both anterolateral and lateral Q waves on ECG).

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Secondary and other clinical outcomes

Table 7. Incidence of secondary outcomes and other outcomes

	Ramipril (N=4645)	Placebo (N=4652)	Hazard ratio* (95% CI)	p-value*
Secondary outcomes				
Revascularization	743 (16.0%)	854 (18.4%)	0.86 (0.78, 0.95)	0.002
Hospitalization for unstable angina	554 (11.9%)	567 (12.2%)	0.98 (0.87, 1.10)	0.67
Hospitalization for heart failure	141 (3.0%)	161 (3.5%)	0.86 (0.69, 1.08)	0.20
Other outcomes (not prespecified)				
Cardiac arrest	37 (0.8%)	59 (1.3%)	0.62 (0.41, 0.94)	0.024
Heart failure**	417 (9.0%)	534 (11.5%)	0.77 (0.68, 0.87)	0.0001
Worsening angina[$]	1010 (21.7%)	1117 (24.0%)	0.88 (0.81, 0.96)	0.005
Hospitalization for unstable angina with ECG changes	175 (3.8%)	180 (3.9%)	0.97 (0.79, 1.19)	0.76

*All deaths are censored at the time of death

** This was a checkbox at every visit on the CRF

[$] Worsening angina was defined a check box on the Unstable Angina Event Form next to the question "Was it increasing in severity or frequency?"

New Diagnosis of Diabetes
(not a prespecified endpoint)

There is a box in the randomization, 1 year follow-up, 2 year follow-up, 3 year follow-up, 4 year follow-up, 5 year follow-up, and penultimate forms for checking to indicate whether a patient is diabetic. Based on these data, the following table is constructed to summarize the new diabetes in the patients who did not have diabetes at baseline. There were a total of 257 new diabetic cases. Ramipril appeared to yield a greater reduction in the incidence of new diabetes. Of the 257 new diabetic cases, only 35 had primary clinical outcomes (cardiovascular death, MI, stroke). The correlation between development of new diabetes and primary clinical outcomes is almost zero. The correlation between time to new diabetes and time to primary clinical outcomes is < 0.15. Both treatment groups show the same correlation pattern. Therefore, new diagnosis of diabetes is an endpoint independent of the primary clinical outcome in the patients who did not have diabetes at baseline. This makes interpretation of the nominal p-value of new diabetes difficult.

Table 8. Incidence of new diagnosis of diabetes in patients who did not have diabetes at baseline

	Ramipril (N=2837) n (%)	Placebo (N=2883) n (%)	Hazard ratio* (95% CI)	p-value*
New diagnosis of diabetes	102 (3.6%)	155 (5.4%)	0.66 (0.51, 0.85)	0.001

*All deaths are censored at the time of death

By vitamin E results

The beneficial effects of ramipril in reducing the incidence of the composite events appear to be similar between vitamin E and no vitamin E strata (Table 9).

Table 9. Incidence of primary outcome by vitamin E stratification

	Ramipril n (%)	Placebo n (%)	Hazard ratio (95% CI)	p-value
Vitamin E group				
Cardiovascular death, MI, Stroke	338 (14.5%)	421 (18.2%)	0.76 (0.66, 0.89)	0.0003
All-cause death, MI, Stroke	424 (18.2%)	497 (21.5%)	0.83 (0.73, 0.95)	0.006
No Vitamin E group				
Cardiovascular death, MI, Stroke	313 (13.5%)	405 (17.3%)	0.79 (0.68, 0.91)	0.0009
All-cause death, MI, Stroke	398 (17.2%)	495 (21.1%)	0.79 (0.70, 0.91)	0.0006