Prescribing information as of XXXX

DRAFT

ALTACE® Capsules

(ramipril)

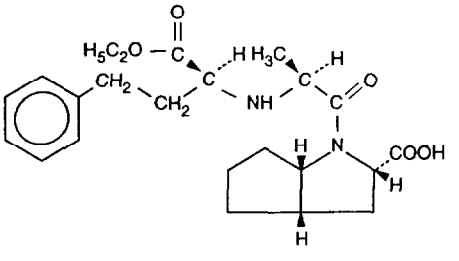
USE IN PREGNANCY

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 elimination 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.

Pharmacodynamics and Clinical Effects

Prevention of Myocardial Infarction, Stroke or Death from Cardiovascular Causes

The Heart Outcomes Prevention Evaluation study (HOPE study)[1] was a large, multi-center, random-

ized, controlled, 2x2 factorial design, double-blind study conducted in 9541 patients (4645 on ALTACE) who were 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). This study was designed to examine the long-term (mean of five years) effects of ALTACE (10 mg orally once a day) on the primary endpoint of myocardial infarction, stroke or death from cardiovascular causes, and the secondary endpoints of death from any cause, the need for coronary artery revascularization, and hospitalization for unstable angina or heart failure.

The HOPE study results showed that ALTACE (10 mg/day) significantly reduced the composite of myocardial infarction, stroke or death from cardiovascular causes (651/4645 *vs.* 826/4652, relative risk 0.78, P<0.001).

Outcome	**Altace (N=4645)** no. (%)	**Placebo (N=4652)**	**Relative Risk (95% CI)**
Combined End-point			
(MI, stroke, or death from CV cause)	651 (14.0%)	826 (17.8%)	0.78 (0.70-0.86), P<0.001
Component End-point			
Death from Cardiovascular Causes	282 (6.1%)	377 (8.1%)	0.74 (0.64-0.87), P<0.001
Myocardial infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70-0.90), P<0.001
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56-0.84), P<0.001
Overall Mortality (Death from any Cause)	482 (10.4%)	569 (12.2%)	0.84 (0.75-0.95), P=0.005

This effect reached significance early in the study and significant differences between active and control continued to be observed throughout the study.

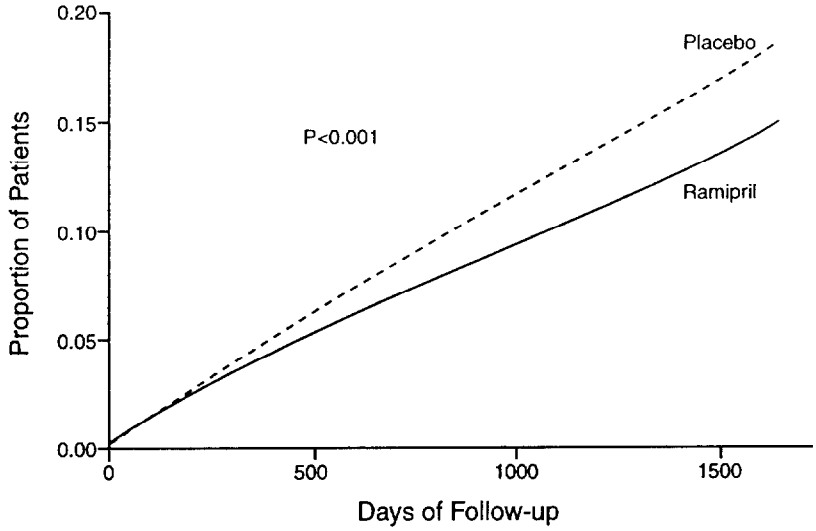
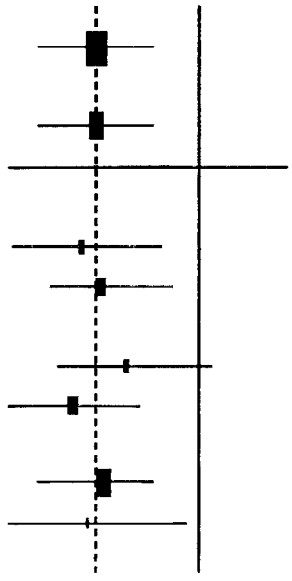


Figure 1: Kaplan-Meier Estimates of the composite outcome of MI, Stroke, or Death from CV causes in the Ramipril Group and the Placebo Group. The relative risk of the composite outcomes in the Ramipril Group as compared with the Placebo Group was 0.78% (95% confidence interval, 0.70-0.86).

The HOPE results were observed in all of the following subgroups:

- Patients with and without hypertension at base line,
- Patients with and without diabetes,
- Men and women;
- Patients with and without evidence of cardiovascular disease,
- Patients who were older or younger than 65 years, and
- Patients with and without microalbuminuria.

	No. of Patients	Incidence of Composite Outcome in Placebo Group
Overall	9297	17.8
Cardiovascular disease	8162	18.7
No cardiovascular disease	1135	10.2
Diabetes	3577	19.8
No diabetes	5720	16.5
Age <65 yr	4169	14.2
Age >65 yr	5128	20.7
Male sex	6817	18.7
Female sex	2480	14.4



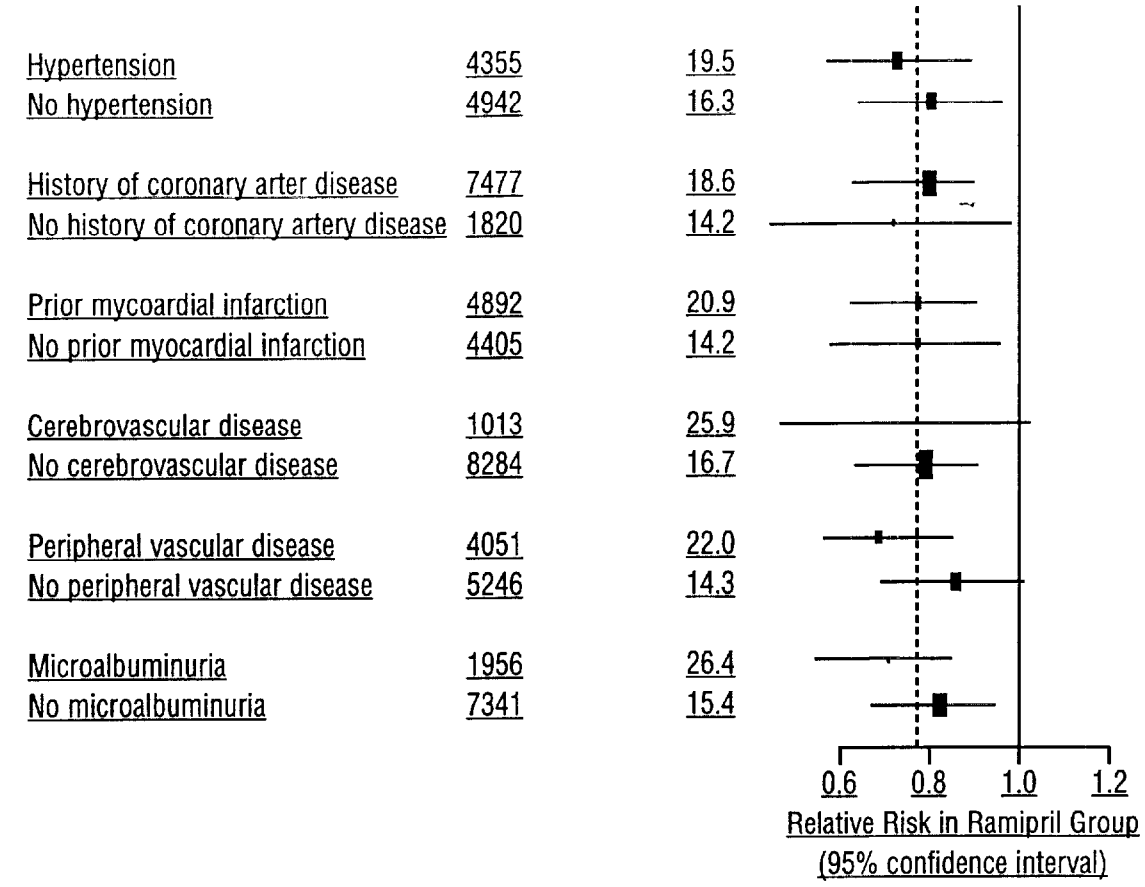


Figure 2. The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Predefined Subgroups. Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is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

The significant benefits of ALTACE were observed among patients who were prescribed and taking the treatments already proven to reduce the risk of cardiovascular events [i.e.; aspirin or other anti-platelet agents (75.3%), beta-blockers (39.2%), and lipid-lowering agents (28.4%)] as well as diuretics (15.3%) and calcium channel blockers (46.3%).

It was calculated that the overall incremental reduction in blood pressure attributable to the addition of ALTACE contributed only marginally to the results of the HOPE study since the majority of patients were not hypertensive at baseline and the reduction in blood pressure with ALTACE during the study was extremely small (3/2 mmHg).

Prespecified Secondary Endpoints of Clinical Relevance

The HOPE study also showed that Altace significantly reduced the number of patients who underwent coronary revascularization (742/4645 vs. 852/4652, rr = 0.85, P=0.002), and there was a trend toward fewer hospitalizations for heart failure (141 vs. 160; rr = 0.88; P = 0.25). In addition, Altace

reduced the incidence of cardiac arrest (37 vs. 59; rr= 0.62; p = 0.02), heart failure (417 vs. 535; rr = 0.77; p<0.001), newly diagnosed diabetes (102 vs. 155; rr = 0.66; p<0.001) and complications related to diabetes (299 vs. 354; rr = 0.84; p = 0.03) as shown in the following table.

Outcome	Altace (N=4645) no. (%)	Placebo (N=4652)	Relative Risk (95% CI)
Secondary Outcomes*			
Revascularization	742 (16.0%)	852 (18.3%)	0.85 (0.77-0.94), P=0.002
Complications Related to Diabetes❖◆	299 (6.4%)	354 (7.6%)	0.88 (0.70-0.98), P=0.03
Hospitalization for Heart Failure	141 (3.0%)	160 (3.4%)	0.88 (0.70-1.10), p=0.25
Other Clinical Relevant Outcomes			
Heart Failure◆	417 (9.0%)	535 (11.5%)	0.77 (0.67-0.87), P<0.001
Cardiac Arrest	37 (0.8%)	59 (1.3%)	0.62 (0.41-0.94), p=0.02
New Diagnosis of Diabetes	102 (3.6%)	155 (5.4%)	0.66 (0.51-0.85) P<0.001

* These events were centrally adjudicated

◆ All cases (with or without hospitalization)

❖ Includes diabetic nephropathy (urinary albumin >300mg/day or urine protein of 500 mg/day), need for dialysis, or need for laser therapy of diabetic retinopathy

Clinical Benefits in Diabetics

In the Microalbuminuria, Cardiovascular, and Renal Outcomes substudy (MICRO-HOPE) of HOPE study,[2] the effects of ALTACE (10 mg orally once a day) on the risk of occurrence of myocardial infarction, stroke or death from cardiovascular causes, and development of overt nephropathy (24 hour urine albumin > 300mg/day, 24 hour urine total protein > 500 mg/day, or albumin/creatinine ratio > 36 mg/mmol + clinical evidence of proteinuria) was investigated in 3577 diabetics in a large, multi-center, two by two factorial designed study. Diabetes status was established by history and physical examination at each visit. Participants were judged to have type 2 diabetes if they developed diabetes at age 30 years or older and did not require insulin for control. Glycated hemoglobin (HbA_{1c}) expressed as the percentage higher than the upper limit of normal and serum creatinine were assayed for participants with a history of diabetes. Urinary albumin excretion was measured at baseline, 1 year, and at the end of study (4.5 years) by determination of albumin/creatinine ratio in a first morning urine specimen. Microalbuminuria was defined as a urine albumine/creatinine ratio equal to or greater than 2mg/mmol. Baseline characteristics of the Altace and placebo groups were similar.

	Ramipril (n=1808)	Placebo (n=1769)
Demography		
Mean age (years)	65.3(6-4)	65.6 (6.6)
Female/male	696 (38%)/ 1112 (62%)	626 (35%)/ 1143 (65%)
Clinical characteristics		
Mean (SD) body-mass index (kg/m²)	28.9 (4.8)	28.6 (4.7)
Mean (SD) heart rate (beats/min)	72.3 (11.4)	72.5 (11.0)
Mean (SD) systolic blood pressure (mm Hg)	141.7 (19.6)	142.3 (19.5)
Mean (SD) diastolic blood pressure (mm Hg)	80 (10.6)	79.3 (10.7)
Mean (SD) ankle/arm systolic pressure (mm Hg)	0.97 (0.19)	0.96 (0.18)
Mean (SD) waist/hip ratio	0.93 (0.09)	0.93 (0.08)
Mean (SD) waist circumference (cm)	99.9 (12.7)	99.6 (12.4)
Microalbuminuria	553 (31%)	587 (33%)
Mean (SD) HbA_{1C} (%)*	123 (30)	124 (32)
Mean (SD) serum creatinine (µmol/L)*	93.8 (22.3)	94.0 (27.6)
Mean duration of diabetes (years)	11.1 (10.2)	11.8 (10.7)
Type 2 diabetes	1774 (98%)	1722 (97%)
History of hypertension	1045 (58%)	951 (54%)
Documented cholesterol >5.2 mmol/L	1174 (65%)	1161 (66%)
Current smoker	274 (15%)	270 (15%)
Previous coronary artery disease	1046 (58%)	1093 (62%)
Previous stroke/endarterectomy	124 (7%)	150 (8%)
Previous peripheral vascular disease	311 (17%)	361 (20%)
No previous cardiovascular disease	604 (33%)	515 (29%)
Hyperglycaemic control		
Dietary therapy alone	331 (18%)	300 (17%)
Insulin therapy alone	432 (24%)	482 (27%)
Oral agents alone	957 (53%)	895 (51%)
Insulin plus oral agents	88 (5%)	92 (5%)
Other Drugs		
Acetylsalicylic acid	982 (54%)	998 (56%)
Diurectics	350 (19%)	350 (20%)
B-blockers	510 (28%)	505 (29%)
Calcium-channel blockers	776 (43%)	801 (45%)
Hypolipidaemic drugs	409 (23%)	390 (22%)

*Measured at local laboratories; HbA_{1C} is reported as percentage above upper limit of normal for local laboratory.

Table 1: **Baseline characteristics of participants with diabetes**

The results of the MICRO-HOPE study showed that in the ramipril treated group, there was a significantly lower rate of occurence of the combined primary endpoint of mycardial infarction, stroke or death from cardiovascular causes (277/1808 vs 351/1769; relative risk reduction=0.25; P=0.0004), as were the secondary endpoints of death from any cause (196 vs 248; relative risk reduction=0.24; P=0.004), the need for coronary artery revascularization (254 vs 291; relative risk reduction=0.17; P=0.031), and development of overt nephropathy (117 vs 149; relative risk reduction=0.24; p=0.027).

Outcome	Altace (N=1808) no. (%)	Placebo (N=1769)	Relative Risk Reduction (95% CI)
Combined End-point			
(MI, stroke, or death from CV cause)	277 (15.3%)	351 (19.8%)	0.25 (0.12-0.36), P=0.0004
Component End-point			
Death from Cardiovascular Causes	112 (6.2%)	172 (9.7%)	0.37 (0.21-0.51), P=0.0001
Myocardial infarction	185 (10.2%)	229 (12.9%)	0.22 (0.06-0.36), P=0.01
Stroke	76 (4.2%)	108 (6.1%)	0.33 (0.10-0.50), P=0.0074
Secondary Outcomes			
Total Mortality	196 (10.8%)	248 (14.0%)	0.24 (0.08-0.37), P=0.004
Revascularization	254 (14.0%)	291 (16.4%)	0.17 (0.02-0.30), P=0.031
Overt Nephropathy❖	117 (6.5%)	149 (8.4%)	0.24 (0.03-0.40), P=0.027
Other Clinical Relevant Outcomes			
Any Heart Failure	198 (11.0%)	236 (13.3%)	0.20 (0.04-0.34), P=0.019
Transient Ischemic Attacks	80 (4.4%)	104 (5.9%)	0.26 (0.01-0.45), P=0.04
Laser Therapy◆	170(9.4%)	186 (10.5%)	0.22 (-0.09-0.28), P=0.24

❖ Based on positive 24 hour urine collection or albumin/creatinine ration > 36 /mmoL if no 24 hour urine available.

◆ Laser therapy for retinopathy

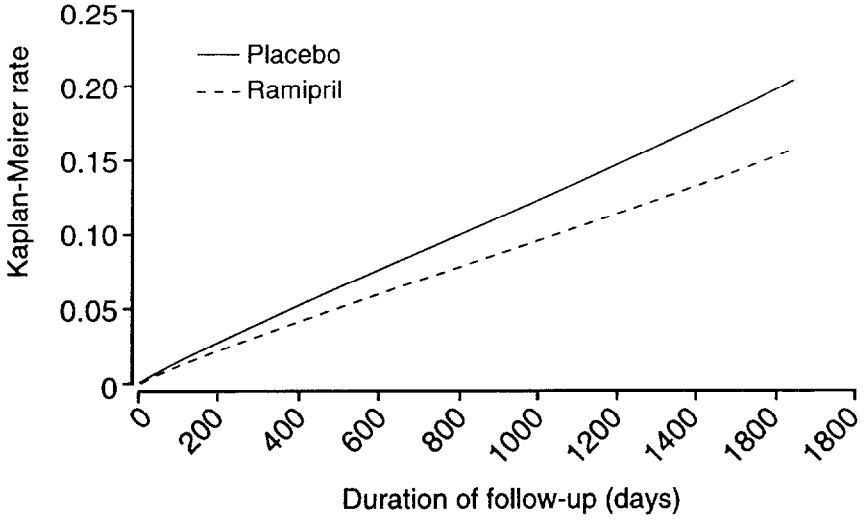


Figure 3: Kaplan-Meier Estimates of the primary outcome of MI, Stroke, or Death from CV causes in the Ramipril Group and the Placebo Group for participants with diabetes. (relative risk reduction 25% [95% CI 12-36], p=0.0004).

During the study, 345 participants developed an albumin/creatinine ratio >36mg/mmol and were asked to provide a urine collection to test for overt nephropathy. Overt nephropathy developed in 117 participants on Altace and 149 on placebo (relative risk redution=0.24, p=0.027). Altace lowered the risk of development of overt nephropathy in both of these groups and in addition led to an albumin/creatinine ratio lower than the placebo group at 1 year and at the end of the study as shown below.

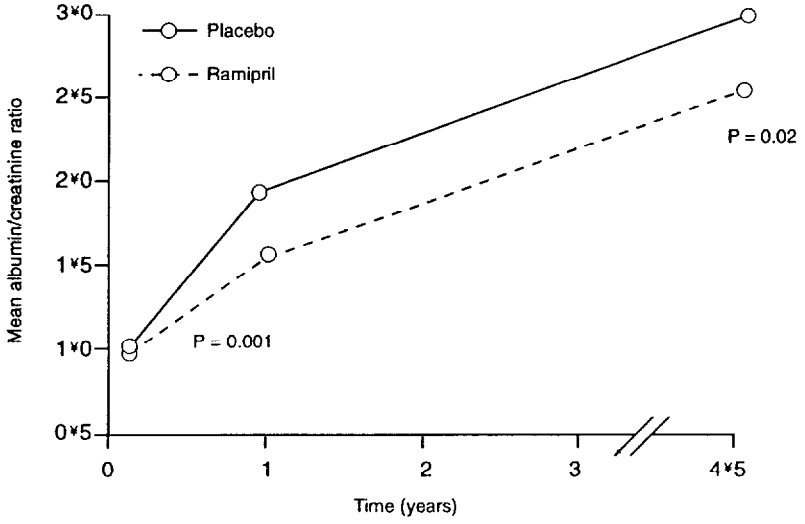


Figure 4: Effect of Altace on degree of albuminuria - Geometric mean albumin/creatinine ratio of all participants with available 24 hr. urine collection. (adjusted for laboratories where assays were performed).

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 influ-

enced 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

Prevention of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

In patients 55 years or older with a history of coronary artery disease, stroke, peripheral vascular

disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), ALTACE is indicated as an adjunctive therapy to significantly reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. In addition, ALTACE is indicated to significantly reduce the incidence of these pre-selected clinically relevant secondary end-points: coronary revascularization procedures, complications related to diabetes, and heart failure.

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 may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 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-aldosterone sys-

tem, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

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

Evaluation of the hypertensive patient should always include assessment of renal function. (See **DOSAGE AND ADMINISTRATION.**)

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE (ramipril). In most cases, 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 syncope 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 insti-

tuted, 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 coadministration 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%).

The 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 are shown below.

PATIENTS IN US PLACEBO CONTROLLED STUDIES

	ALTACE (n=651)		Placebo (n=286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. 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 these 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 with heart failure treated with ALTACE 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	10.7	4.7
Cough Increased	7.6	3.7
Dizziness	4.1	3.2
Angina Pectoris	2.9	2.0
Nausea	2.2	1.4
Postural Hypotension	2.2	1.4
Syncope	2.1	1.4
Heart Failure	2.0	2.2
Severe/Resistance Heart Failure	2.0	3.0

Myocardial Infarct	1.7	1.7
Vomiting	1.6	0.5
Vertigo	1.5	0.7
Headache	1.2	0.8
Kidney Function	1.2	0.5
Abnormal Chest Pain	1.1	0.9
Diarrhea	1.1	0.4
Asthenia	0.3	0.8

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):

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 (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

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**.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See **PRECAUTIONS, Cough** subsection.)

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

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 abnor-

mal 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

Prevention of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

For the prevention 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, followed by 5 mg, once a day for the next 3 weeks, and then increased to a maintenance dose of 10 mg, once a day.

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. A patient who becomes hypotensive at

this dose may be switched to 1.25 mg twice daily, but all patients should then be titrated (as tolerated) toward a target dose of 5 mg twice daily.

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/1.73m^2 (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.

REFERENCE

1.The Heart Outcomes Prevention Evaluation Study Investigators. Effects of An Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. N Engl J Med 2000;342:145-153.

2. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355:253-59.

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