

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 19-901/S-025

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 19-901/S-025

Trade Name: Altace 1.25, 2.5, 5, and 10 mg Capsules

Generic Name: (ramipril)

Sponsor: Hoechst Marion Roussel, Inc.

Approval Date: December 16, 1998

Indication: Provides for revised final printed label.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 19-901/S-025

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 19-901/S-025

DEC 16 1998

Hoechst Marion Roussel, Inc.
Attention: J. Michael Nicholas, Ph.D.
10236 Marion Park Drive
Kansas City, MO 64134-0627

Dear Dr. Nicholas:

Please refer to your supplemental new drug application dated November 16, 1998, received November 17, 1998, 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 note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c) and that the revisions were implemented on October 27, 1998. For future reference, please note that under this section, you are required to submit a supplement at the time you make such changes.

This supplemental new drug application provides for final printed labeling revised as follows:

At the top of the package insert, "910500-6/96" has been replaced with "Prescribing Information as of February 1998." The word "Capsules" has been added. The asterisk following "(ramipril)" has been deleted.

CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism: In the fourth paragraph, second sentence, "are" has been changed to "is," to state "... 60% of the parent drug and its metabolites is eliminated... ."

In the last sentence of the last paragraph, the word "of" has been changed to "on," to state "... the effect of a given dose on plasma ACE activity... ."

PRECAUTIONS, Hyperkalemia: "(ramipril)" has been added after "ALTACE" in the first sentence. The word "(ramipril)" was present in the labeling approved with the last supplement, S-019, but it was deleted in the package insert included in the March 26, 1998 annual report.

ADVERSE REACTIONS, Miscellaneous: "Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported." has been added.

ADVERSE REACTIONS, Hypertension: In the table, the word "ALTACE" in the column heading is now in all caps.

ADVERSE REACTIONS, Hypertension and Heart Failure post-myocardial infarction: "N" has been changed to "n." in the column headings of the tables.

At the bottom of the package insert, the statement "Caution: Federal law prohibits dispensing without prescription." has been replaced with "Rx only." The asterisk preceding the patent information has been deleted. "ALTACE REG TM HOECHST AG" has been deleted. "Prescribing Information as of February 1998." has been added. The corporate web site "www.hmri.com" has been added.

The word "(ramipril)" has been deleted after "ALTACE" in the following locations:
CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism, in the first sentence of the first paragraph; **WARNINGS, Hypotension**, in the first sentence of the first paragraph; **PRECAUTIONS, Nursing Mothers**, in the first sentence; and **ADVERSE REACTIONS, Heart failure post-myocardial infarction, Renal**.

In addition, a hyphen has been inserted in the phrase "post-myocardial infarction" in the following locations:

INDICATIONS, Heart Failure post-myocardial infarction, in the heading and in the text; **DOSAGE AND ADMINISTRATION, Heart Failure post-myocardial infarction**, in the heading and in the subheading under "Dosage Adjustment in Renal Impairment."

Other minor editorial revisions have been made throughout the insert.

We have completed the review of this supplemental application 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 final printed labeling included in your November 16, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

RJL 12/16/95

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

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cc:

Archival NDA 19-901

HFD-110/Div. Files

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-101/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-95/DDMS (with labeling)

HFD-810/DNDC Division Director

DISTRICT OFFICE

HFD-110/K.Bongiovanni

sb/12/2/98;12/8/98

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approval date: 1/28/91

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-901/S-025

FINAL PRINTED LABELING

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 ALTA CE 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 ALTA CE 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 vasodilator peptide, play a role in the therapeutic effects of ALTA CE remains to be elucidated. While the mechanism through which ALTA CE lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ALTA CE has an antihypertensive effect even in patients with low-renin hypertension. Although ALTA CE was antihypertensive in all races studied, black hypertensive patients (mainly a low-renin hypertensive population) had a smaller average response to monotherapy than non-black patients.

Pharmacokinetics and Metabolism

Following oral administration of ALTA CE, 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 ALTA CE capsules or the contents of identical capsules dissolved in water, dissolved in apple juice, or suspended in apple sauce, serum ramipril levels were essentially unrelated to the use or nonuse of the concomitant liquid for 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 75% and that of ramiprilat about 56%, *in vitro*, these percentages are independent of concentration over the range of 0.01 to 10 µg/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 excreted in the feces 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 ramipril, 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. 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 ALTA CE, 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 ramipril 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 80-80% inhibition of ACE activity 4 hours after dosing with approximately 40-60% inhibition after 24 hours. Multiple oral doses of ramipril of 20 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

Hypertension
Administration of ALTA CE to patients with mild to moderate hypertension results in a reduction in both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypoten-

sion is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See WARNINGS.) Use of ALTA CE in combination with a thiazide diuretic gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5-20 mg of ALTA CE 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. od 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 ALTA CE increased during the first several weeks of repeated measurements. The antihypertensive effect of ALTA CE has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ALTA CE has not resulted in a rapid increase in blood pressure.

ALTA CE 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.

ALTA CE was less effective in blacks than in caucasians. The effectiveness of ALTA CE 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

ALTA CE 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 ALTA CE 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, and 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 either of these 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 ALTA CE 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 ALTA CE 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

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

In usual ALTA CE 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 ALTA CE does not have a similar risk. (See WARNINGS.) In considering use of ALTA CE, 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 late readmission, 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

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

WARNINGS

Angioedema 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 ALTA CE) 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 ALTA CE should be discontinued and appropriate therapy instituted immediately. Where there is involvement of the tongue, pharynx, or larynx, likely to cause airway obstruction, appropriate treatment is a 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 angioedema, 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

ALTA CE can cause symptomatic hypotension, after either the initial dose or a later dose if 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, diarrheas, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTA CE.

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, ALTA CE 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. ALTA CE 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 ALTA CE 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 intra-uterine environment.

If oligohydramnios is observed, ALTA CE 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. ALTA CE which crosses the placenta can be removed from the neonatal circulation by such means, but limited experience has not shown that such removal is central to the treatment of these infants. No teratogenic effects of ALTA CE 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 system, 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 ALTA CE, 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

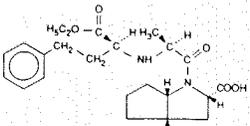
Prescribing Information as of February 1998

ALTA CE Capsules (ramipril)

ALTA CE 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 (2S,3aS,6aS)-1[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]amino]octahydrocyclopropanoic acid (2-pyrrolidone-2-carboxylic acid, 1-ethyl ester; its structural formula is:

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, ALTA CE 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 (2S,3aS,6aS)-1[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]amino]octahydrocyclopropanoic acid (2-pyrrolidone-2-carboxylic acid, 1-ethyl ester; its structural formula is:



Its empirical formula is C₂₃H₃₂N₂O₅, and its molecular weight is 416.5. Ramipril, the diacid metabolite of ramipril, is a non-sulphydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group. ALTA CE (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

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.)

Hypertension: 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, usually 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, 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 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 administered 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, diopans, antiacid, 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 detectable 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 ramipril 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

Adverse Event	ALTACE (n=651)		Placebo (n=266)	
	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

Adverse Event	Placebo-Controlled (AIRE) Mortality Study	
	Ramipril (n=1004)	Placebo (n=982)
Hypertension	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 reported 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, tremor, 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.)

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, urea 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.

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, urea 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 an effective hypotensin, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

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 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 of 1.25 mg or less 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.

ALTACE® (ramipril)

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 0039-0103-10), and Unit Dose packs of 100 (NDC 0039-0103-11).

ALTACE 2.5 mg capsules are supplied as orange, hard gelatin capsules in bottles of 100 (NDC 0039-0104-10), Unit Dose packs of 100 (NDC 0039-0104-11), and Bulk pack of 5000's (NDC 0039-0104-80).

ALTACE 5 mg capsules are supplied as red, hard gelatin capsules in bottles of 100 (NDC 0039-0105-10), Unit Dose packs of 100 (NDC 0039-0105-11), and Bulk pack of 5000's (NDC 0039-0105-80).

ALTACE 10 mg capsules are supplied as Process Blue, hard gelatin capsules in bottles of 100 (NDC 0039-0106-10).

Dispense in well-closed container with safety closure. Store at controlled room temperature (59 to 86° F).

Rx only.

Prescribing Information as of February 1998

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