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15 November 2005

The United States Food & Drug Administration  
Division of Dockets Management (HFA-305)  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852  
BY COURIER

Re: Docket No. 2005P- (Citizens Petition for RAMIPRIL)

Dear Sirs :

The captioned drug product is approved as an immediate release solid oral dosage form (a capsule). Enclosed find the original and three copies of a CITIZEN'S PETITION seeking approval for a new dosage form (a tablet).

Please let me know if you require any further information. Many thanks in advance for your help. With my very best regards,

PHARMACEUTICAL PAENT ATTORNEYS, LLC

  
J. Mark POHL  
Direct +1 (973) 984 0076  
*Mark.Pohl@LicensingLaw.Net*

Mbc:mp  
Enclosure  
Cc w/enclosure :

Arianne CAMPHIRE, Ph.D., Office of Generic Drugs

2005P-0472

CPI

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: THE UNITED STATES  
: FOOD & DRUG  
: ADMINISTRATION  
  
: *In re* ramipril 1.25, 2.50, 5.00  
: And 10.00 milligram instant-release  
: oral tablets  
:  
: **CITIZEN'S PETITION**  
:  
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This is a Citizen's Petition submitted pursuant to the Administrative Procedure Act, United States Code, Title 5, The Federal Food, Drug & Cosmetic Act, United States Code, Title 21, § 505(j)(2)(C), and the Code of Federal Regulations, Title 21, § 10.30 (2005).

Action Requested

This Petition requests the Commissioner of the Food & Drug Administration make a determination that:

A. the drug product ramipril instant release oral tablets, in the strengths of 1.25, 2.50, 5.00 and 10.00 milligrams is suitable for consideration in an Abbreviated New Drug Application.

2005P-0472

CP 1

Statement of Grounds for Relief

The Reference Listed Drug

The reference listed drug product is Altace® brand ramipril instant release oral capsules in the strengths of 1.25, 2.50, 5.00 and 10.00 milligrams. The reference listed drug is an angiotensin converting enzyme (ACE) inhibitor. See 1998 version of FDA approved labeling text for Altace® brand ramipril tablets at page 1, column 1 (16 December 1998) (copy attached). The reference listed drug is the subject of New Drug Application No. 01-9901, approved on 28 January 1991. At the present time, the Holder of that New Drug Application is King Pharmaceuticals, Inc., of Bristol, Tennessee.

The NDA approval for the reference listed drug has not been withdrawn due to safety nor efficacy concerns. To the contrary, it was approved for use on 28 January 1991, and since that time has enjoyed a record of safety and effectiveness which supported its approval for additional labeled indications. See Robert TEMPLE, M.D., Letter (4 October 2000) (approving the reference listed drug for a new labeled indication); see also New Drug Application No. 01-9901 Supplement No. 010 (22 August 1995) (approving a new labeled indication for the reference listed drug).

The reference listed drug is currently approved for use in, *inter alia*, the reduction of the risk of myocardial infarction, stroke, and death from cardiovascular causes. *Id.*

The reference listed drug is approved for sale as an immediate release capsule. The reference listed drug is approved for sale in four strengths: 1.25, 2.50, 5.00 and 10.00 milligrams. See United States Food & Drug Administration, Electronic Orange Book entry for Altace® brand ramipril instant release oral capsules (15 November 2005) (copy attached).

The Proposed New Dosage Form

An Abbreviated New Drug Application may be filed for the approval of a new drug product that is the same as the reference listed drug. *See* 21 U.S.C.A. § 355(j)(2)(A) (2005). An Abbreviated New Drug Application may also be filed for a new drug product which is the same as the reference listed drug except for a difference in dosage form, if the Commissioner grants permission to file such an Application by making an administrative finding that the difference in dosage form is suitable. *See* 21 U.S.C.A. § 355(j)(2)(C) (2005); 21 C.F.R. § 314.93(b). The Commissioner has authority to approve a Citizen's Petition seeking a change in dosage form. *See* 21 C.F.R. § 10.25, 10.30 (2005).

Petitioner respectfully requests the Commissioner make a determination that ramipril immediate release oral tablet drug product is suitable for consideration in an Abbreviated New Drug Application, in the same strengths for which the reference listed drug is available in capsule form.

There is no reason to question the safety and effectiveness of the proposed drug product dosage form for its labeled uses. As noted above, the reference listed drug has enjoyed a record of safety and effectiveness which supported its approval for additional labeled indications.

These proposed drug products will contain the same active drug substance as the reference listed drug, have the same route of administration (oral) as the reference listed drug, will have the same delivery mechanism (immediate release), and have the same dosage strengths (1.25, 2.5, 5 and 10 milligram). The labeling of the proposed drug product will also be the same as the currently-approved labeling for the reference listed drug, except for changes which are required because of the difference in manufacturer

and the difference in dosage form proposed under this Petition. The proposed products will differ from the reference listed drug only in their dosage form.

Approval of this Citizen's Petition is respectfully believed warranted because the Food & Drug Administration routinely approves Suitability Petitions asking for a change from one immediate release oral dosage form to another immediate release oral dosage form where there is no other change in labeling, route of administration, active drug substance, dosage strength, et cetera. For the foregoing reasons, Petitioner respectfully believes that the proposed dosages are suitable for approval under an Abbreviated New Drug Application.

Request to Waive Pediatric Assessment

An assessment of the safety and efficacy of the product in pediatric patients is required for any application for a new active ingredient, dosage form, indication, route of administration or dosing regimen. See 21 U.S.C. § 355B(A)(4)(ii) (2004).

This Petition does not request any change in active ingredient, dosage strength, indication, route of administration, nor dosing regimen. The dosing regimen – the amount of drug the patient will be administered, and when, and for what symptoms, and with what co-administered therapeutics - will remain the same as the dosing regimen currently-approved for the reference listed drug. This Petition proposes changing the form from capsule to tablet, not changing the drug dosing regimen which those tablets are used for. Petitioner therefore respectfully believes that this Petition does not require pediatric assessment.

In the alternative, Petitioner requests waiver of pediatric assessment, because the Agency has waived and deferred the pediatric assessments for the reference listed drug. *See* Robert TEMPLE, M.D., Letter at page 2 (4 October 2000) ("We are waiving the pediatric study requirement for this action on this application."). Petitioner therefore respectfully believes that a full waiver of pediatric studies is warranted.

Environmental Impact

Petitioner respectfully believes that it need not submit environmental impact information, because such information is categorically excluded from Suitability Petitions. *See* 21 C.F.R. § 25.31.

Economic Impact

Petitioner respectfully believes that it need not submit economic impact information unless requested to do so by the Commissioner. *See* 21 C.F.R. § 10.30(b).

Action Requested

Petitioner respectfully requests the Commissioner make a determination that:

- A. the drug product ramipril instant release oral tablets, in the strengths of 1.25, 2.50, 5.00 and 10.00 milligrams is suitable for consideration in an Abbreviated New Drug Application.
- B. this dosage form is either exempt from the requirement for pediatric assessment, or that is subject to assessment and the requirement is waived.

Certification

The undersigned certifies that, to the best of its knowledge and belief, this Citizen's Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to this Petition.

Respectfully Submitted,  
PHARMACEUTICAL PATENT ATTORNEYS, LLC

By:   /s/  

Mark Pohl, Esq.  
55 Madison Avenue, 4<sup>th</sup> floor  
Morristown, NJ 07960-7397  
Direct Dial (973) 984-0076

Enclosures

Enclosures

- 1) FDA approved labeling text for Altace® brand ramipril tablets (16 December 1998).
- 2) Robert TEMPLE, M.D., Letter (4 October 2000).
- 3) United States Food & Drug Administration, Electronic Orange Book entry for Altace® brand ramipril oral capsules (15 November 2005).

## Proprietary Name Search Results from "OB\_Rx" table for query on "Altace."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
<u>019901</u>	AB	No	RAMIPRIL	CAPSULE; ORAL	1.25MG	ALTACE	KING PHARMS
<u>019901</u>	AB	Yes	RAMIPRIL	CAPSULE; ORAL	10MG	ALTACE	KING PHARMS
<u>019901</u>	AB	No	RAMIPRIL	CAPSULE; ORAL	2.5MG	ALTACE	KING PHARMS
<u>019901</u>	AB	No	RAMIPRIL	CAPSULE; ORAL	5MG	ALTACE	KING PHARMS

[Return to Electronic Orange Book Home Page](#)

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FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through October, 2005

Patent and Generic Drug Product Data Last Updated: November 15, 2005

OCT 4 2000

NDA 19-901/S-028

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

Dear Mr. Rogers:

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

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

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

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

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

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

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

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

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

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

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

If you have any questions, please call:

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

Sincerely,



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

# APPROVED

DEC 16 1998

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 ALTAEC 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 ALTAEC 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 a decrease 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. Whenever increased levels of bradykinin, a potent vasodilator peptide, play a role in the therapeutic effects of ALTAEC, this role is not anticipated.

While the mechanism through which ALTAEC lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ALTAEC has an antihypertensive effect even in patients with low-renin hypertension. Although ALTAEC 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 ALTAEC, peak plasma concentrations of ramipril are reached within 2 hours. 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 ALTAEC 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 or food.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diastereoisomer. Peak plasma concentrations of ramipril are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilol about 56%; *in vitro*, these percentages are independent of concentration over the range of 0.1 to 10 µg/ml.

Ramipril is almost completely metabolized to ramiprilol, which has about 6 times the ACE inhibitory activity of ramipril, and to the diastereoisomeric ester, the diastereoisomeric acid, and the glucuronide of ramipril and ramiprilol, all of which are inactive. After oral administration of ramipril, about 60% of the administered dose is eliminated in the urine, and about 40% is found in the feces. About 50% of the administered dose is recovered in urine as unchanged ramipril. Blood concentrations of ramipril and ramiprilol increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilol, however, is dose-proportional over the 2.5-20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilol were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously. Plasma concentrations of ramiprilol 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, ramiprilol shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilol 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 ramiprilol/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 ramiprilol concentrations within the therapeutic range was 13-17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilol are reached by the fourth dose. Steady-state concentrations of ramiprilol are somewhat higher than those seen after the first dose of ALTAEC, especially at low doses (2.5 mg), but the difference is clinically insignificant. In patients with creatinine clearance less than 40 mL/min/1.73m<sup>2</sup>, peak levels of ramiprilol are approximately doubled, and trough levels may be as much as quintupled. In multiple-dose regimens, the total exposure to ramiprilol (AUC) in these patients is 3-4 times as large as it is in patients with normal renal function who receive similar doses.

The primary excretion of ramipril, ramiprilol, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 mL/min/1.73m<sup>2</sup> had higher peak and trough ramiprilol levels and slightly longer half-lives. Peak concentrations of ramiprilol 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 pronounced effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilol and relatively slow release from those sites.

**Pharmacodynamics and Clinical Effects**  
Administration of ALTAEC to patients with mild to moderate hypertension results in a reduction of both systolic and diastolic 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 sensitive to vasodilation. (See WARNINGS.) Use of ALTAEC 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 ALTAEC lowered blood pressure within 1-2 hours, with peak reductions achieved 2-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In long-term (4-12 weeks) controlled studies, once-daily doses of 2.5-10 mg were similar in their effect, lowering systolic or diastolic blood pressure 24 hours after dosing by about 64 mm Hg more than placebo. In both comparisons of peak vs. trough effect, the trough effect represented about 50-60% of the peak response. In a fibrinogen 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 ALTAEC increased during the first several weeks of repeated measurement. The antihypertensive effect of ALTAEC has been shown to continue at least 2 years after treatment for at least 2 years. Abrupt withdrawal of ALTAEC has not resulted in a rapid increase in blood pressure.

ALTAEC has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and diuretics 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 reported. 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. In contrast, ALTAEC was less effective in blacks than in Caucasians. The effectiveness of ALTAEC 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 serum uric acid in healthy volunteers. Renal glomerular filtration rate was unchanged.

**Heart Failure post-myocardial infarction**

ALTAEC was studied in the Acute Infarction Ramipril Efficacy Study (ARIES). This was a multinational (mainly European) 161-center, double-blind, randomized, parallel-group study comparing ALTAEC (2.5 mg bid) 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 I-IV) heart failure, patients with unstable angina, and patients with contraindications to ACE inhibitors were 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 5.6 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 3-68). The use of ALTAEC was associated with a 27% reduction (p<0.02) in the risk of death from any cause; about 90% of the deaths that occurred were cardiovascular, mainly sudden death. The rate of progression to severe heart failure and of CHF-related hospitalization were also reduced, by 23% (p<0.01) and 26% (p<0.01), respectively. The benefits of ALTAEC therapy were seen in both genders, and they were not affected by the exact timing of the start of therapy, but older patients may have had a greater benefit than younger ones. The benefits were similar in patients on and not on various concomitant medications; at the time of randomization these included aspirin (about 80% of patients), diuretics (about 80%), organic nitrates (about 55%), beta-blockers (about 20%), calcium channel blockers (about 15%), and digoxin (about 12%).

**INDICATIONS AND USAGE**

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

In the treatment of hypertension, consideration should be given to the fact that, as with other angiotensin-converting enzyme inhibitors, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTAEC does not have a similar risk. (See WARNINGS.)

In controlled trials of ALTAEC, it should be noted that in patients with hypertension, the effect of ramipril 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 7 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 risk of failure-related hospitalization and progression to severe/irreversible heart failure. (See CLINICAL PHARMACOLOGY, Heart Failure post-myocardial infarction for details and limitations of the survival trial.)

**CONTRAINDICATIONS**  
ALTAEC is contraindicated in patients who are hypersensitive to the product and to 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 alicyclopropanes and polypeptides, including angiotensin, bradykinin, patients receiving ACE inhibitors including ALTAEC 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 associated with receiving an ACE inhibitor. (See also CONTRAINDICATIONS.)  
Angioedema of the face, extremities, lips, tongue, pharynx, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal edema or angioedema of the face, tongue, or pharynx occurs,

treatment with ALTAEC should be discontinued and appropriate therapy instituted immediately. Where there is involvement of the tongue, pharynx, or larynx, heavy to coarse airway obstruction, appropriate therapy, a 9% sodium citrate solution 1.1, 0.90 (0.5 ml to 1.0 ml) should be promptly administered. (See ADVERSE REACTIONS.)

In a large U.S. postmarketing study, angioedema (defined as edema of the tongue, larynx, tongue, or throat) was reported in 21/523 (0.20%) of black patients and in 8/858 (0.09%) of white patients. These rates were not different statistically.

**Anaphylactoid reactions during desensitization:** Two patients undergoing desensitization 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 rescheduling.

**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 adsorption.

**Hypotension**  
ALTAEC 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, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTAEC.

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, ALTAEC 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. ALTAEC 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 or bone marrow depression. Clinicians should be alert to the possibility of neutropenia 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; deaths in infants in the setting has been associated with fetal lung hypoplasia, cranial ossification defects, 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 while receiving ACE inhibitors they should discontinue the use of ALTAEC 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, ALTAEC 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 diuresis in fetal-neonatal ALTAEC which crosses the placenta can be removed from the newborn by dialysis by these means, but limited experience has not shown that such removal is central to the treatment of these infants. No teratogenic effects of ALTAEC 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 renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTAEC, 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

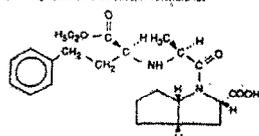
## ALTAEC® Capsules (ramipril)

### 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, ALTAEC 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 87323-19-5. Ramipril's chemical name is (2S,3aS,6S)-1[(S)-N-(1S)-1-carboxy-3-silyloxypropyl]amino-2-hydroxyoctahydrocyclopenta [b]pyrroline-2-carboxylic acid, 1-ethyl ester; its structural formula is:



Its empirical formula is C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>, and its molecular weight is 416.5. Ramiprilol, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilol by hepatic cleavage of the ester group. ALTAEC (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 active 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 ramiprilol inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a

creatinine may occur. Experience with another angiotensin converting enzyme inhibitor, lisinopril, has shown that increases in serum creatinine are usually reversible upon discontinuation of ACE inhibitor 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 ACE inhibitor has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ACE inhibitor 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.)

**Hypotension:** In clinical trials, hypotension (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 trial because of hypotension. Risk factors for the development of hypotension include renal insufficiency, diuretic therapy, 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 ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibition-induced cough should be considered in the differential diagnosis of cough.

**Impaired Liver Function:** Since ramipril is primarily metabolized by hepatic enzymes to its active moiety, ramiprilol, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been conducted 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 secondarily 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 be related to the use of intravenous ACE inhibitor solutions 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 the condition has been resolved by their 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 patient recovers.

All patients should be cautioned that excessive 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.

**Hypertension:** 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-sparing diuretics and potassium-sparing diuretics:** ALTACE can increase potassium levels 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, digoxin, alcohol, furosemide, dantrolene, indomethacin, and flunitrazepam. 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 effect of the latter drug. Additionally, co-administration of ALTACE with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anticoagulation.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**  
**Carcinogenesis:** 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 doses 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 ramiprilol levels and area under the plasma concentration time curve (AUC) for ramiprilol 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 1,102 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 0% 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=553)		Placebo (n=286)	
	n	%	n	%
Headache	35	6.4	17	5.9
"Dizziness"	14	2.5	9	3.1
Asthenia (Fatigue)	13	2.0	7	2.7
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. At 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 (fatal and nonfatal 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	4.7
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	0.9
Vertigo	1.5	0.7
Headache	1.2	0.8
Kidney Function	1.2	0.9
Abnormal Chest Pain	1.1	0.5
Diarrhea	1.1	0.4
Asthenia	0.3	0.3

Other adverse experiences reported in controlled clinical trials (in less than 1% of patients) in relation to possible postmarketing experience, include the following (in some a causal relationship to drug use is uncertain).

**Body As a Whole:** Anaphylactoid reactions (See WARNINGS); Cervicofacial: 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.) Angiotensin II 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.)

**GI/Gastrointestinal:** Exacerbation of 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 (renewed onset), depression, hearing loss, insomnia, nervousness, neuropathy, paraesthesia, somnolence, linnitus, tinnitus, vertigo, and vision disturbances.

**Miscellaneous:** As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANK, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia,

photosensitivity, rash and other dermatologic manifestations. Association of ALTACE with other ACE inhibitors, angiotensin antagonists has been reported.

**Female/male infertility and sterility:** 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. Increase in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 5% 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 impairment 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 few were mild) and a decrease of 2 units or 5% respectively were also observed 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 results of laboratory tests: 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 incidences of leukopenia, eosinophilia, and prothrombin. In US trials, less than 0.2% of patients discontinuing 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, to any extent, no established role in the management of ramipril overdosage. 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 whether any of these substances can be readily removed from the body by hemodialysis. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of ramipril overdosage, but angiotensin II is presently unavailable outside of specialized research facilities. Because the hypotensive effect of ramipril is achieved through vasodilation and systemic hypovolemia, it is reasonable to treat ramipril overdosage by infusion of normal saline solution.

**DOSAGE AND ADMINISTRATION**  
**Hypertension:**

The recommended initial dose for patients not receiving a diuretic is 2.5 mg twice 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-myocardial 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 be treated (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 absence 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 broken and the contents sprinkled on a small amount (about one) 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 dosing mixture 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 initially 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<sup>2</sup> (serum creatinine approximately >2.5 mg/dL) doses only 25% of those normally used should be expected to induce their therapeutic levels of ramiprilol. (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 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 bottles 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), and 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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Made in USA  
 US Patent 4,587,258  
 5001M800