DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020184/S-015 **SUPPLEMENT APPROVAL**

Abbott Products, Inc.
Attention: Kenny Seaver, RAC
Manager
Global Pharmaceutical Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Seaver:

Please refer to your supplemental new drug application dated June 30, 2009, received July 1, 2009, submitted under section 505(b)1 of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aceon (perindopril erbumine) Tablets.

This "Prior-Approval" supplemental new drug application provides for revision to the labeling of Aceon with the following content changes:

This supplement provides for the conversion of the Aceon label to the Physician Labeling Rule (PLR) format. Editorial changes were made throughout the label; specific content changes are listed below.

In the **Boxed Warning**:

From

USE IN PREGNANCY
When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ACEON ® Tablets should be discontinued as soon as possible.

To

WARNING: AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue ACEON as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury to or death of the developing fetus.

In **INDICATIONS AND USAGE**

Deleted

When using ACEON, consideration should be given to the fact that another angiotensin converting enzyme (ACE) inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to determine whether ACEON has a similar potential. (See **WARNINGS**)

In considering use of ACEON, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblack patients. In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to nonblack patients. (See **WARNINGS**: ***Head and Neck Angioedema.***)

In the **DOSAGE AND ADMINISTRATION** section:

From

Hypertension

Use in Uncomplicated Hypertensive Patients

In patients with essential hypertension, the recommended initial dose is 4 mg once a day. The dosage may be titrated upward until blood pressure, when measured just before the next dose, is controlled or to a maximum of 16 mg per day. The ususal maintenance dose range is 4 to 8 mg administered as a single daily dose. ACEON Tablets may also be administered in two divided doses. When once-daily dosing was compared to twice-daily dosing in clinical studies, the B.I.D. regime was generally slightly superior, but not by more than about 0.5 to 1.0 mmHG.

Use in the Elderly Patients

As in younger patients, the recommended initial dosage of ACEON Tablets for the elderly (>65 years) is 4 mg daily, given in one or two divided doses. The daily dosage may be titrated upward until blood pressure, when measured just before the next dose, is controlled, but experience with ACEON Tablets is limited in the elderly at doses exceeding 8 mg. Dosages above 8 mg should be administered with caution and under close medical supervision. (See **PRECAUTIONS: Geriatric Use.**)

Use in Concomitant Diuretics

If blood pressure is not adequately controlled with perindopril alone, a diuretic may be added. In patients currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of perindopril. To reduce likelihood of such reaction, the diuretic should, if possible, be discontinued 2 to 3 days prior to the beginning of ACEON Tablets therapy. (See **WARNINGS**) Then, if blood pressure is not controlled with ACEON Tablets alone, the diuretic should be resumed.

If the diuretic cannot be discontinued, an initial dose of 2 to 4 mg daily in one or in two divided doses should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage should then be titrated as described above. (See **WARNINGS** and **PRECAUTIONS: Drug Interactions**.)

After the first dose of ACEON Tablets the patient should be followed closely for the first two weeks of treatment and whenever the dose of ACEON Tablets and/or diuretics is increased (See **WARNINGS** and **PRECAUTIONS: Drug Interactions**.) In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ACEON Tablets. To reduce the likelihood of hypotension, the dose of diuretic, if possible, can be adjusted which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ACEON Tablets does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

To

2.1 Hypertension

Use in Uncomplicated Hypertensive Patients: In patients with essential hypertension, the recommended initial dose is 4 mg once a day. The dose may be titrated, as needed to a maximum of 16 mg per day. The usual maintenance dose range is 4 mg to 8 mg administered as a single daily dose or in two divided doses.

Use in Elderly Patients: The recommended initial daily dosage of ACEON for the elderly is 4 mg daily, given in one or two divided doses. Experience with ACEON is limited in the elderly at doses exceeding 8 mg. Dosages above 8 mg should be administered with careful blood pressure monitoring and dose titration. *[see Use in Specific Populations (8.5)]*.

Use with Diuretics: In patients who are currently being treated with a diuretic, symptomatic hypotension can occur following the initial dose of ACEON. Consider reducing the dose of diuretic prior to starting ACEON *[see Drug Interactions (7.1)]*.

AND

From

Dose Adjustment in Renal Impairment

Kinetic data indicate that perindoprilat elimination is decreased in renally impaired patients, with a marked increase in accumulation when creatinine clearance drops below 30 mL/min. In such patients (creatinine clearance <30 ml/min), safety and efficacy of ACEON Tablets have not been established. For patients with lesser degrees of impairment (creatinine clearance above 30 mL/min), the initial dosage should be 2 mg/day and dosage should not exceed 8 mg/day due to limited clinical experience. During dialysis, perindopril is removed with the same clearance as in patients with normal renal function.

To

2.3 Dose Adjustment in Renal Impairment and Dialysis

Perindoprilat elimination is decreased in renally impaired patients. ACEON is not recommended in patients with creatinine clearance <30 mL/min. For patients with lesser degrees of impairment, the initial dosage should be 2 mg/day and dosage should not

exceed 8 mg/day. During dialysis, perindopril is removed with the same clearance as in patients with normal renal function.

Dosage Forms and Strengths section was added

In the **CONTRAINDICATIONS** section:

Added

ACEON is contraindicated in patients known to be hypersensitive (including angioedema) to this product or to any other ACE inhibitor. ACEON is also contraindicated in patients with hereditary or idiopathic angioedema.

In the **WARNINGS AND PRECAUTIONS** section:

The subsections were re-ordered.

From

5.1 ***Anaphylactoid and Possibly Related Reactions*** Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ACEON) may be subject to a variety of adverse events, some of them serious.

Head and Neck Angioedema: Angioedema involving the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including ACEON (0.1% of patients treated with ACEON in U.S. clinical trials). In such cases, ACEON should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with involvement of the tongue, glottis or larynx may be fatal due to airway obstruction. Appropriate therapy, such as subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL), should be promptly administered. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

To

5.1 ***Anaphylactoid and Possibly Related Reactions***
Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ACEON) may be subject to a variety of adverse events, some of them serious. Black patients receiving ACE inhibitors have a higher incidence of angioedema compared to nonblacks.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, or larynx has been reported in patients treated with ACE inhibitors, including ACEON (0.1% of patients treated with ACEON in U.S. clinical trials). Angioedema associated with involvement of the tongue, glottis or larynx may be fatal. In such cases, discontinue

ACEON treatment immediately and observe until the swelling disappears. When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, administer appropriate therapy, such as subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL), promptly.

And

Deleted

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.

And

From

5.2 ***Hypotension***

Like other ACE inhibitors, ACEON can cause symptomatic hypotension. ACEON has been associated with hypotension in 0.3% of uncomplicated hypertensive patients in U.S. placebo-controlled trials. Symptoms related to orthostatic hypotension were reported in another 0.8% of patients.

Symptomatic hypotension associated with the use of ACE inhibitors is more likely to occur in patients who have been volume and/or salt-depleted, as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ACEON. *[See Dosage and Administration (2.1)]*.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitors may cause excessive hypotension, and may be associated with oliguria or azotemia, and rarely with acute renal failure and death. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

In patients at risk of excessive hypotension, ACEON therapy should be started under very close medical supervision. Patients should be followed closely for the first two weeks of treatment and whenever the dose of ACEON and/or diuretic is increased.

If excessive hypotension occurs, the patient should be placed immediately in a supine position and, if necessary, treated with an intravenous infusion of physiological saline.

ACEON treatment can usually be continued following restoration of volume and blood pressure.

5.3 ***Neutropenia/Agranulocytosis***
Another ACE 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 patients with a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ACEON are insufficient to show whether ACEON causes agranulocytosis at similar rates.

To

5.2 ***Hypotension***
ACEON can cause symptomatic hypotension. ACEON has been associated with hypotension in 0.3% of uncomplicated hypertensive patients in U.S. placebo-controlled trials. Symptoms related to orthostatic hypotension were reported in another 0.8% of patients.

Symptomatic hypotension is most likely to occur in patients who have been volume or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting *[see Dosage and Administration (2.1)]*.

ACE inhibitors may cause excessive hypotension, and may be associated with oliguria or azotemia, and rarely with acute renal failure and death. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

In patients at risk of excessive hypotension, ACEON therapy should be started under very close medical supervision. Patients should be followed closely for the first two weeks of treatment and whenever the dose of ACEON and/or diuretic is increased.

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

5.3 ***Neutropenia/Agranulocytosis***
ACE inhibitors have been associated with agranulocytosis and bone marrow depression, most frequently in patients with renal impairment, especially patients with a collagen vascular disease such as systemic lupus erythematosus or scleroderma.

And

From

5.5 ***Impaired Renal Function***
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals.

To

5.5 ***Impaired Renal Function***

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. Renal function should be monitored periodically in patients receiving ACEON. *[see Dosage and Administration (2.3)]*.

In patients with severe congestive heart failure, where renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACEON, may be associated with oliguria, progressive azotemia, and, rarely, acute renal failure and death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur; usually reversible upon discontinuation of the ACE inhibitor. In such patients, renal function should be monitored during the first few weeks of therapy.

Some ACEON-treated patients have developed minor and transient increases in blood urea nitrogen and serum creatinine especially in those concomitantly treated with a diuretic.

And

Deleted

5.7 ***Hypertensive Patients with Congestive Heart Failure***

In patients with severe congestive heart failure, where renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACEON, may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death.

5.8 ***Hypertensive Patients with Renal Artery Stenosis***

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with ACE inhibitors suggests that these increases are usually reversible upon discontinuation of the drug. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients without apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient. These increases are more likely to occur in patients treated concomitantly with a diuretic and in patients with pre-existing renal impairment. Reduction of dosages of ACEON, the diuretic or both may be required. In some cases, discontinuation of either or both drugs may be necessary.

Evaluation of hypertensive patients should always include an assessment of renal function. *[See Dosing and Administration (2.3)]*.

And

From

5.*9* ***Hyperkalemia***
Elevations of serum potassium have been observed in some patients treated with ACE inhibitors, including ACEON. In U.S. controlled clinical trials, 1.4% of the patients receiving ACEON and 2.3% of patients receiving placebo showed increased serum potassium levels greater than 5.7 mEq/L. Most cases were isolated single values that did not appear clinically relevant and were rarely a cause for withdrawal. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus and the concomitant use of agents such as potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Drugs associated with increases in serum potassium should be used cautiously, if at all, with ACEON. *[See Drug Interactions (7.2)]*.

5.10 ***Cough***
Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials with perindopril, cough was present in 12% of perindopril patients and 4.5% of patients given placebo.

To

5.6 ***Hyperkalemia***
Elevations of serum potassium have been observed in some patients treated with ACE inhibitors, including ACEON. Most cases were isolated single values that did not appear clinically relevant and were rarely a cause for withdrawal. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus and the concomitant use of agents such as potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes *[see Drug Interactions (7.2)]*.

Serum potassium should be monitored periodically in patients receiving ACEON.

5.7 ***Cough***
Presumably because of the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, generally resolving after discontinuation of therapy. Consider ACE inhibitor-induced cough in the differential diagnosis of cough.

In the **ADVERSE REACTIONS** section:

Added

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

AND

From

6.1 Hypertension

ACEON has been evaluated for safety in approximately 3,400 patients with hypertension in U.S. and foreign clinical trials. ACEON was in general well-tolerated in the patient populations studied, the side effects were usually mild and transient. Although dizziness was reported more frequently in placebo patients (8.5%) than in perindopril patients (8.2%), the incidence appeared to increase with an increase in perindopril dose.

The data presented here are based on results from the 1,417 ACEON-treated patients who participated in the U.S. clinical trials. Over 220 of these patients were treated with ACEON for at least one year.

In placebo-controlled U.S. clinical trials, the incidence of premature discontinuation of therapy due to adverse events was 6.5% in patients treated with ACEON and 6.7% in patients treated with placebo. The most common causes were cough, headache, asthenia and dizziness.

Among 1,012 patients in placebo-controlled U.S. trials, the overall frequency of reported adverse events was similar in patients treated with ACEON and in those treated with placebo (approximately 75% in each group). Table 1 shows adverse events that occurred in 1% or greater of the patients and that were more common for perindopril than placebo by at least 1% (regardless of whether they were considered to be related to study drug) in the first two columns below. Of these adverse events, those considered possibly or probably related to study drug are shown in the last two columns.

Table 1:
Frequency of Adverse Events (%)

	All Adverse Events		**Possibly– or Probably–Related Adverse Events**	
	Perindopril n=789	Placebo n=223	Perindopril n=789	Placebo n=223
Cough	12	4.5	6	1.8
Back Pain	5.8	3.1	0	0
Sinusitis	5.2	3.6	0.6	0
Viral Infection	3.4	1.6	0.3	0
Upper Extremity Pain	2.8	1.4	0.2	0
Hypertonia	2.7	1.4	0.2	0
Dyspepsia	1.9	0.9	0.3	0
Fever	1.5	0.5	0.3	0
Proteinuria	1.5	0.5	1	0.5
Ear Infection	1.3	0	0	0
Palpitation	1.1	0	0.9	0

Of these, cough was the reason for withdrawal in 1.3% of perindopril and 0.4% of placebo patients. While dizziness was not reported more frequently in the perindopril group (8.2%) than in the placebo group (8.5%), it was clearly increased with dose, suggesting a causal relationship with perindopril. Other commonly reported complaints (1% or greater), regardless of causality, include: headache (23.8%), upper respiratory infection (8.6%), asthenia (7.9%), rhinitis (4.8%), low extremity pain (4.7%), diarrhea (4.3%), edema (3.9%), pharyngitis (3.3%), urinary tract infection (2.8%), abdominal pain (2.7%), sleep disorder (2.5%), chest pain (2.4%), injury, paresthesia, nausea, rash (each 2.3%), seasonal allergy, depression (each 2%), abnormal ECG (1.8%), ALT increase (1.7%), tinnitus, vomiting (each 1.5%), neck pain, male sexual dysfunction (each 1.4%), triglyceride increase, somnolence (each 1.3%), joint pain, nervousness, myalgia, menstrual disorder (each 1.1%), flatulence and arthritis (each 1%), but none of those was more frequent by at least 1% on perindopril than on placebo. Depending on the specific adverse event, approximately 30 to 70% of the common complaints were considered possibly or probably related to treatment.

Below is a list (by body system) of adverse events reported in 0.3 to 1% of patients in U.S. placebo-controlled studies in hypertensive patients without regard to attribution to therapy. Less frequent but medically important adverse events are also included; the incidence of these events is given in parentheses.

Body as a Whole: malaise, pain, cold/hot sensation, chills, fluid retention, orthostatic symptoms, anaphylactic reaction, facial edema, angioedema (0.1%).

Gastrointestinal: constipation, dry mouth, dry mucous membrane, appetite increased, gastroenteritis.

Respiratory: posterior nasal drip, bronchitis, rhinorrhea, throat disorder, dyspnea, sneezing, epistaxis, hoarseness, pulmonary fibrosis (<0.1%).

Urogenital: vaginitis, kidney stone, flank pain, urinary frequency, urinary retention.

Cardiovascular: hypotension, ventricular extrasystole, myocardial infarction, vasodilation, syncope, abnormal conduction, heart murmur, orthostatic hypotension.

Endocrine: gout.

Hematology: hematoma, ecchymosis.

Musculoskeletal: arthralgia, myalgia.

CNS: migraine, amnesia, vertigo, cerebral vascular accident (0.2%).

Psychiatric: anxiety, psychosexual disorder.

Dermatology: sweating, skin infection, tinea, pruritus, dry skin, erythema, fever blisters, purpura (0.1%).

Special Senses: conjunctivitis, earache.

Laboratory: potassium decrease, uric acid increase, alkaline phosphatase increase, cholesterol increase, AST increase, creatinine increase, hematuria, glucose increase.

When ACEON was given concomitantly with thiazide diuretics, adverse events were generally reported at the same rate as those for ACEON alone, except for a higher incidence of abnormal laboratory findings known to be related to treatment with thiazide diuretics alone (*e.g.*, increases in serum uric acid, triglycerides and cholesterol and decreases in serum potassium).

6.2 Stable Coronary Artery Disease

Perindopril has been evaluated for safety in EUROPA, a double-blind, placebo-controlled study in 12,218 patients with stable coronary artery disease. The overall rate of discontinuation was about 22% on drug and placebo. The most common medical reasons for discontinuation that were more frequent on perindopril than placebo were cough, drug intolerance and hypotension.

To

6.1 *Clinical Trials Experience*

The following adverse reactions are discussed elsewhere in labeling:

- Anaphylactoid reactions, including angioedema *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Neutropenia and agranulocytosis *[see Warnings and Precautions (5.3)]*
- Impaired renal function *[see Warnings and Precautions (5.5)]*
- Hyperkalemia *[see Warnings and Precautions (5.6)]*
- Cough *[see Warnings and Precautions (5.7)]*

Hypertension

ACEON has been evaluated for safety in approximately 3,400 patients with hypertension in U.S. and foreign clinical trials. The data presented here are based on results from the 1,417 ACEON-treated patients who participated in the U.S. clinical trials. Over 220 of these patients were treated with ACEON for at least one year.

In placebo-controlled U.S. clinical trials, the incidence of premature discontinuation of therapy due to adverse events was 6.5% in patients treated with ACEON and 6.7% in patients treated with placebo. The most common causes were cough, headache, asthenia and dizziness.

Among 1,012 patients in placebo-controlled U.S. trials, the overall frequency of reported adverse events was similar in patients treated with ACEON and in those treated with placebo (approximately 75% in each group). The only adverse events whose incidence on ACEON was at least 2% greater than on placebo were cough (12% vs. 4.5%) and back pain (5.8% vs. 3.1%).

Dizziness was not reported more frequently in the perindopril group (8.2%) than in the placebo group (8.5%), but its likelihood increased with dose, suggesting a causal relationship with perindopril.

Stable Coronary Artery Disease
Perindopril has been evaluated for safety in EUROPA, a double-blind, placebo-controlled study in 12,218 patients with stable coronary artery disease. The overall rate of discontinuation was about 22% on drug and placebo. The most common medical reasons for discontinuation that were more frequent on perindopril than placebo were cough, drug intolerance and hypotension.

AND

From

Potential Adverse Effects Reported with ACE Inhibitors: Other medically important adverse effects reported with other available ACE inhibitors include: cardiac arrest, eosinophilic pneumonitis, neutropenia/agranulocytosis, pancytopenia, anemia (including hemolytic and aplastic), thrombocytopenia, acute renal failure, nephritis, hepatic failure, jaundice (hepatocellular or cholestatic), symptomatic hyponatremia, bullous pemphigoid, pemphigus, acute pancreatitis, falls, psoriasis, exfoliative dermatitis and a syndrome which may include: arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermatologic manifestations, a positive ANA, leukocytosis, eosinophilia or an elevated ESR. Many of these adverse effects have also been reported for perindopril.

To

6.2 Postmarketing Experience

Voluntary reports of adverse events in patients taking ACEON that have been received since market introduction and are of unknown causal relationship to ACEON include: cardiac arrest, eosinophilic pneumonitis, neutropenia/agranulocytosis, pancytopenia, anemia (including hemolytic and aplastic), thrombocytopenia, acute renal failure, nephritis, hepatic failure, jaundice (hepatocellular or cholestatic), symptomatic hyponatremia, bullous pemphigoid, pemphigus, acute pancreatitis, falls, psoriasis, exfoliative dermatitis and a syndrome which may include: arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermatologic manifestations, a positive antinuclear antibody (ANA), leukocytosis, eosinophilia or an elevated erythrocyte sedimentation rate (ESR).

And

Deleted

6.3 Clinical Laboratory Test Findings
Hypertension: Hematology, clinical chemistry and urinalysis parameters have been evaluated in U.S. placebo-controlled trials. In general, there were no clinically significant trends in laboratory test findings.

Hyperkalemia: In clinical trials, 1.4% of the patients receiving ACEON and 2.3% of the patients receiving placebo showed serum potassium levels greater than 5.7 mEq/L. *[See Warnings and Precautions (5.9)]*.

BUN/Serum Creatinine Elevations: Elevations, usually transient and minor, of BUN and serum creatinine have been observed. In placebo-controlled clinical trials, the proportion of patients experiencing increases in serum creatinine were similar in the ACEON and placebo treatment groups. Rapid reduction of long-standing or markedly elevated blood pressure by any antihypertensive therapy can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine. *[See Warnings and Precautions (5.8)]*.

And

From

7.1 ***Diuretics***
Patients on diuretics, and especially those started recently, may occasionally experience an excessive reduction of blood pressure after initiation of ACEON therapy. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with perindopril. If diuretics cannot be interrupted, close medical supervision should be provided with the first dose of ACEON, for at least two hours and until blood pressure has stabilized for another hour. *[See Warnings and Precautions (5.2)]*.

The rate and extent of perindopril absorption and elimination are not affected by concomitant diuretics. The bioavailability of perindoprilat was reduced by diuretics, however, and this was associated with a decrease in plasma ACE inhibition.

7.2 *Potassium Supplements and Potassium-Sparing Diuretics*
ACEON may increase serum potassium because of its potential to decrease aldosterone production. Use of potassium-sparing diuretics (spironolactone, amiloride, triamterene and others), potassium supplements or other drugs capable of increasing serum potassium (indomethacin, heparin, cyclosporine and others) 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.

7.3 *Lithium*
Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium concentration is recommended. Use of a diuretic may further increase the risk of lithium toxicity.

To

7.1 *Diuretics*
Patients on diuretics, and especially those started recently, may occasionally experience an excessive reduction of blood pressure after initiation of ACEON therapy. The possibility of hypotensive effects can be minimized by either decreasing the dose of or discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with perindopril. If diuretic therapy cannot be altered, provide close medical supervision with the first dose of ACEON, for at least two hours and until blood pressure has stabilized for another hour *[see Warnings and Precautions (5.2)]*.

The rate and extent of perindopril absorption and elimination are not affected by concomitant diuretics. The bioavailability of perindoprilat was reduced by diuretics, however, and this was associated with a decrease in plasma ACE inhibition.

7.2 ***Potassium Supplements and Potassium-Sparing Diuretics***

ACEON may increase serum potassium because of its potential to decrease aldosterone production. Use of potassium-sparing diuretics (spironolactone, amiloride, triamterene and others), potassium supplements or other drugs capable of increasing serum potassium (indomethacin, heparin, cyclosporine and others) can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, monitor the patient's serum potassium frequently.

7.3 ***Lithium***

Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. Frequent monitoring of serum lithium concentration is recommended. Use of a diuretic may further increase the risk of lithium toxicity.

And

Deleted

7.7 ***Food Interaction***

Oral administration of ACEON with food does not significantly lower the rate or extent of perindopril absorption relative to the fasted state. However, the extent of biotransformation of perindopril to the active metabolite, perindoprilat, is reduced approximately 43%, resulting in a reduction in the plasma ACE inhibition curve of approximately 20%, probably clinically insignificant. In clinical trials, perindopril was generally administered in a non-fasting state.

In the **USE IN SPECIFIC POPULATIONS** section:

From

(b) (4)

8.3 Nursing Mothers

Milk of lactating rats contained radioactivity following administration ^{14}C-perindopril. It is not known whether perindopril is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ACEON is given to nursing mothers.

To

8.1 ***Pregnancy***

Pregnancy Category D *[see Boxed Warning and Warnings and Precautions (5.4)]*. Radioactivity was detectable in fetuses after administration of ^{14}C-perindopril to pregnant rats.

8.3 Nursing Mothers

Milk of lactating rats contained radioactivity following administration of ^{14}C-perindopril. It is not known whether perindopril is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ACEON is given to nursing mothers.

And

From

8.5 Geriatric Use

(b) (4) The mean blood pressure effect of perindopril was somewhat smaller in patients over 60 than in younger patients, although the difference was not significant. Plasma concentrations of both perindopril and perindoprilat were increased in edlerly patients compared to concentrations in younger patients. No adverse effects were clearly increased in older patients with the exception of dizziness and possibly rash.

Perindopril should be used with caution when administered to elderly patients who are at an increased risk for falls due to age, their underlying disease and/or their concurrent use of medication(s) associated with falls. Falls and fall-related events may be exacerbated by the central nervous system effects of dizziness and syncope as well as the symptomatic hypotension, including orthostatic, associated with perindopril. Experience with ACEON in elderly patients at daily doses exceeding 8 mg is limited. (b) (4)

To

8.5 *Geriatric Use*

The mean blood pressure effect of perindopril was somewhat smaller in patients over 60 than in younger patients, although the difference was not significant. Plasma concentrations of both perindopril and perindoprilat were increased in edlerly patients compared to concentrations in younger patients. No adverse effects were clearly increased in older patients with the exception of dizziness and possibly rash.

Start at a low dose and titrate slowly as needed. Monitor for dizziness because of potential for falls.

Experience with ACEON in elderly patients at daily doses exceeding 8 mg is limited.

In the **OVERDOSAGE** section:

Added

Among the reported cases of perindopril overdosage, patients who were known to have ingested a dose of 80 mg to 120 mg required assisted ventilation and circulatory support. One additional patient developed hypothermia, circulatory arrest and died following ingestion of up to 180 mg of perindopril. The intervention for perindopril overdose may require vigorous support.

In the **CLINICAL PHARMACOLOGY** section:

From

Absorption: Oral administration of ACEON results in its rapid absorption with peak plasma concentrations occurring at approximately 1 hour. The absolute oral bioavailability of perindopril is about 75%. Following absorption, approximately 30 to 50% of systemically available perindopril is hydrolyzed to its active metabolite, perindoprilat, which has a mean bioavailability of about 25%. Peak plasma concentrations of perindoprilat are attained 3 to 7 hours after perindopril administration. The presence of food in the gastrointestinal tract does not affect the rate or extent of absorption of perindopril but reduces bioavailability of perindoprilat by about 35%. *[See Drug Interactions (7.7)]*.

With 4 mg, 8 mg and 16 mg doses of ACEON, Cmax and AUC of perindopril and perindoprilat increase in a linear and dose-proportional manner following both single oral dosing and at steady state during a once-a-day multiple dosing regimen.

Distribution: Approximately 60% of circulating perindopril is bound to plasma proteins, and only 10 to 20% of perindoprilat is bound. Therefore, drug interactions mediated through effects on protein binding are not anticipated.

At usual antihypertensive dosages, little radioactivity (less than 5% of the dose) was distributed to the brain after administration of ^{14}C-perindopril to rats. Radioactivity was detectable in fetuses and in milk after administration of ^{14}C-perindopril to pregnant and lactating rats.

Metabolism and Elimination: Perindopril exhibits multiexponential pharmacokinetics following oral administration. The mean half-life of perindopril associated with most of its elimination is approximately 0.8 to 1 hours. At very low plasma concentrations of perindopril (less than 3 ng/mL), there is a prolonged terminal elimination half-life, similar to that seen with other ACE inhibitors, that results from slow dissociation of perindopril from plasma/tissue ACE binding sites. Perindopril does not accumulate with a once-a-day multiple dosing regimen. Mean total body clearance of perindopril is 219 to 362 mL/min and its mean renal clearance is 23.3 to 28.6 mL/min.

Perindopril is extensively metabolized following oral administration, with only 4 to 12% of the dose recovered unchanged in the urine. Six metabolites resulting from hydrolysis, glucuronidation and cyclization via dehydration have been identified. These include the active ACE inhibitor, perindoprilat (hydrolyzed perindopril), perindopril and perindoprilat glucuronides, dehydrated perindopril and the diastereoisomers of dehydrated perindoprilat. In humans, hepatic esterase appears to be responsible for the hydrolysis of perindopril.

The active metabolite, perindoprilat, also exhibits multiexponential pharmacokinetics following the oral administration of ACEON. Formation of perindoprilat is gradual with peak plasma concentrations occurring between 3 and 7 hours. The subsequent decline in plasma concentration shows an apparent mean half-life of 3 to 10 hours for the majority of the elimination, with a prolonged terminal elimination half-life of 30 to 120 hours resulting from slow dissociation of perindoprilat from plasma/tissue ACE binding sites. During repeated oral oncedaily dosing with perindopril, perindoprilat accumulates about 1.5 to 2 fold and attains steady state plasma levels in 3 to 6 days. The clearance of perindoprilat and its metabolites is almost exclusively renal.

To

12.3 ***Pharmacokinetics***

Absorption: Oral administration of ACEON results in peak plasma concentrations that occur at approximately 1 hour. The absolute oral bioavailability of perindopril is about 75%. Following absorption, approximately 30 to 50% of systemically available perindopril is hydrolyzed to its active metabolite, perindoprilat, which has a mean bioavailability of about 25%. Peak plasma concentrations of perindoprilat are attained 3 to 7 hours after perindopril administration. Oral administration of ACEON with food does not significantly lower the rate or extent of perindopril absorption relative to the fasted state. However, the extent of biotransformation of perindopril to the active metabolite, perindoprilat, is reduced approximately 43%, resulting in a reduction in the plasma ACE inhibition curve of approximately 20%, probably clinically insignificant. In clinical trials, perindopril was generally administered in a non-fasting state.

With 4 mg, 8 mg and 16 mg doses of ACEON, Cmax and AUC of perindopril and perindoprilat increase in a dose-proportional manner following both single oral dosing and at steady state during a once-a-day multiple dosing regimen.

Distribution: Approximately 60% of circulating perindopril is bound to plasma proteins, and only 10 to 20% of perindoprilat is bound. Therefore, drug interactions mediated through effects on protein binding are not anticipated.

Metabolism and Elimination: Following oral administration perindopril exhibits multicompartment pharmacokinetics including a deep tissue compartment (ACE binding sites). The mean half-life of perindopril associated with most of its elimination is approximately 0.8 to 1 hours.

Perindopril is extensively metabolized following oral administration, with only 4 to 12% of the dose recovered unchanged in the urine. Six metabolites resulting from hydrolysis, glucuronidation and cyclization via dehydration have been identified. These include the active ACE inhibitor, perindoprilat (hydrolyzed perindopril), perindopril and perindoprilat glucuronides, dehydrated perindopril and the diastereoisomers of dehydrated perindoprilat. In humans, hepatic esterase appears to be responsible for the hydrolysis of perindopril.

The active metabolite, perindoprilat, also exhibits multicompartment pharmacokinetics following the oral administration of ACEON. Formation of perindoprilat is gradual with peak plasma concentrations occurring between 3 and 7 hours. The subsequent decline in

plasma concentration shows an apparent mean half-life of 3 to 10 hours for the majority of the elimination, with a prolonged terminal elimination half-life of 30 to 120 hours resulting from slow dissociation of perindoprilat from plasma/tissue ACE binding sites. During repeated oral once daily dosing with perindopril, perindoprilat accumulates about 1.5 to 2 fold and attains steady state plasma levels in 3 to 6 days. The clearance of perindoprilat and its metabolites is almost exclusively renal.

And

From

Renal Impairment: With perindopril doses of 2 mg to 4 mg, perindoprilat AUC increases with decreasing renal function. At creatinine clearances of 30 to 80 mL/min, AUC is about double that of 100 mL/min. When creatinine clearance drops below 30 mL/min, AUC increases more markedly.

In a limited number of patients studied, perindopril dialysis clearance ranged from 41.7 to 76.7 mL/min (mean 52 mL/min). Perindoprilat dialysis clearance ranged from 37.4 to 91 mL/min (mean 67.2 mL/min). *[See Dosage and Administration (2.3)]*.

To

Renal Impairment: With perindopril erbumine doses of 2 mg to 4 mg, perindoprilat AUC increases with decreasing renal function. At creatinine clearances of 30 to 80 mL/min, AUC is about double that at 100 mL/min. When creatinine clearance drops below 30 mL/min, AUC increases more markedly.

In a limited number of patients studied, perindopril clearance by dialysis ranged from about 40 to 80 mL/min. Perindoprilat clearance by dialysis ranged from about 40 to 90 mL/min. *[see Dosage and Administration (2.3)]*.

In the **CLINICAL STUDIES** section:

From

14.1 Hypertension

In placebo-controlled studies of perindopril monotherapy (2 mg to 16 mgonce daily) in patients with a mean blood pressure of about 150/100 mm Hg, 2 mg had little effect, but doses of 4 mg to 16 mg lowered blood pressure. The 8 mg and 16 mg doses were indistinguishable, and both had a greater effect than the 4 mg dose. The magnitude of the blood pressure effect was similar in the standing and supine positions, generally about 1 mm Hg greater on standing. In these studies, doses of 8 mg and 16 mg per day gave supine, trough blood pressure reductions of 9 to 15/5 to 6 mm Hg. When once daily and twice daily dosing were compared, the twice daily dosing regimen was generally slightly superior, but by not more than about 0.5 mm Hg to 1 mm Hg. After 2 mg to 16 mg doses of perindopril, the trough mean systolic and diastolic blood pressure effects were approximately equal to the peak effects (measured 3 to 7 hours after dosing.). Trough effects were about 75 to 100% of peak effects. When perindopril was given to patients

receiving 25 mg hydrochlorothiazide, it had an added effect similar in magnitude to its effect as monotherapy, but 2 mg to 8 mg doses were approximately equal in effectiveness. In general, the effect of perindopril occurred promptly, with effects increasing slightly over several weeks.

In hemodynamic studies carried out in animal models of hypertension, blood pressure reduction after perindopril administration was accompanied by a reduction in peripheral arterial resistance and improved arterial wall compliance. In studies carried out in patients with essential hypertension, the reduction in blood pressure was accompanied by a reduction in peripheral resistance with no significant changes in heart rate or glomerular filtration rate. An increase in the compliance of large arteries was also observed, suggesting a direct effect on arterial smooth muscle, consistent with the results of animal studies.

Formal interaction studies of ACEON have not been carried out with antihypertensive agents other than thiazides. Limited experience in controlled and uncontrolled trials coadministering ACEON with a calcium channel blocker, a loop diuretic or triple therapy (beta-blocker, vasodilator and a diuretic), does not suggest any unexpected interactions. In general, ACE inhibitors have less than additive effects when given with beta-adrenergic blockers, presumably because both work in part through the renin angiotensin system. A controlled pharmacokinetic study has shown no effect on plasma digoxin concentrations when coadministered with ACEON. *[See Drug Interactions (7.5)]*.

In uncontrolled studies in patients with insulin-dependent diabetes, perindopril did not appear to affect glycemic control. In long-term use, no effect on urinary protein excretion was seen in these patients.

The effectiveness of ACEON was not influenced by sex and it was less effective in black patients than in nonblack patients. In elderly patients (greater than or equal to 60 years), the mean blood pressure effect was somewhat smaller than in younger patients, although the difference was not significant.

To

14.1 *Hypertension*

In placebo-controlled studies of perindopril monotherapy (2 mg to 16 mg once daily) in patients with a mean blood pressure of about 150/100 mm Hg, 2 mg had little effect, but doses of 4 mg to 16 mg lowered blood pressure. The 8 mg and 16 mg doses were indistinguishable, and both had a greater effect than the 4 mg dose. In these studies, doses of 8 mg and 16 mg per day gave supine, trough blood pressure reductions of 9 to 15/5 to 6 mm Hg. When once daily and twice daily dosing were compared, the twice daily dosing regimen was generally slightly superior, but by not more than about 0.5 mm Hg to 1 mm Hg. After 2 mg to 16 mg doses of perindopril, the trough mean systolic and diastolic blood pressure effects were about 75 to 100% of peak effects.

Perindopril's effects on blood pressure were similar when given alone or on a background of 25 mg hydrochlorothiazide In general, the effect of perindopril occurred promptly, with effects increasing slightly over several weeks.

Formal interaction studies of ACEON have not been carried out with antihypertensive agents other than thiazides. Limited experience in controlled and uncontrolled trials coadministering ACEON with a calcium channel blocker, a loop diuretic or triple therapy (beta-blocker, vasodilator and a diuretic), does not suggest any unexpected interactions. In general, ACE inhibitors have less than additive effects when given with beta-adrenergic blockers, presumably because both work in part through the renin angiotensin system.

In uncontrolled studies in patients with insulin-dependent diabetes, perindopril did not appear to affect glycemic control. In long-term use, no effect on urinary protein excretion was seen in these patients.

The effectiveness of ACEON was not influenced by sex and it was less effective in black patients than in nonblack patients. In elderly patients (greater than or equal to 60 years), the mean blood pressure effect was somewhat smaller than in younger patients, although the difference was not significant.

In the **HOW SUPPLIED/STORAGE AND HANDLING** section:

From

Tablets	Appearance	NDC (Bottles of 100)
2 mg	Scored one side, white, oblong (debossed "ACN 2" on one side and debossed with "SLV" on both sides of score on the other side)	NDC 0032-1101-01
4 mg	Scored one side, pink, oblong (debossed "ACN 4" on one side and debossed with "SLV" on both sides of score on the other side)	NDC 0032-1102-01
8 mg	Scored one side, salmon-colored, oblong (debossed "ACN 8" on one side and debossed with "SLV" on both sides of score on the other side)	NDC 0032-1103-01

To

Tablets are oblong and debossed on both halves of the scored side with “SLV”.

Tablets	Appearance	NDC (Bottles of 100)
2 mg	White, debossed “ACN 2” on unscored side	NDC 0032-1101-01
4 mg	Pink, debossed “ACN 4” on unscored side	NDC 0032-1102-01
8 mg	Salmon-colored, debossed “ACN 8” on unscored side	NDC 0032-1103-01

In the **PATIENT COUNSELING INFORMATION** section:

From

(b) (4)

[redacted]

(b) (4)

[redacted]

[redacted]

[redacted]

To

Inform female patients of childbearing age that use of drugs, such as ACEON, that act on the renin-angiotensin system during pregnancy may cause serious problems in the fetus and infant. Patients taking ACEON who are or plan to become pregnant should immediately notify their healthcare provider.

Tell patients to report immediately signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, hoarseness or difficulty in swallowing or breathing) and to take no more drug before consulting a healthcare provider.
Tell patients to report promptly any indication of infection (*e.g.*, sore throat, fever) which could be a sign of neutropenia.

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Agreed upon labeling text

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
12/10/2010