CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020184 / S003

Trade Name : ACEON CAPSULES

Generic Name: Perindoppril Erbumine Capsules 2mg, 4mg and 8mg Capsules

Sponsor : Rhone Poulenc Roher

Approval Date: January 8, 1997

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APPLICATION 020184/S003

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020184/S003

APPROVAL LETTER

F97-8398

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-184/S-003

JAN 8 1997

Rhône-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Ronald F. Panner
500 Arcola Road
Collegeville, PA 19426-0107

Dear Mr. Panner:

Please refer to your November 15, 1996 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aceon (perindopril erbumine) 2, 4, and 8 mg Capsules.

The supplemental application provides for final printed labeling revised as follows:

INDICATIONS AND USAGE: As we requested in our January 27, 1995 Supplement Request letter, the following has been added:

> 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 nonblacks. 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 nonblacks. (see **WARNINGS: Angioedema**.)

WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid reactions during membrane exposure: The phrase " (a procedure dependent upon devices not approved in the United States)" has been deleted, as we requested in our facsimile transmission on March 8, 1996.

PRECAUTIONS, Pediatric Use: The word "children" has been replaced with "pediatric patients."

HOW SUPPLIED: The storage conditions have been revised to comply with the CDER Stability Committee Uniform Storage Statement. In addition, the sentence "ACEON is a product of Servier Research" and the Rhone-Poulenc Rorer signature line have been added.

We note that except for the changes above, the labeling is as we requested in the approval letter of December 30, 1993.

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

We note the following minor errors in the package insert. Please make corrections at the time of your next printing. These changes should be described in your annual report and not submitted as a supplement.

CLINICAL PHARMACOLOGY, Mechanism of Action: In the first paragraph, third sentence, the word "vasoconstriction" should be changed to "vasoconstrictor."

CLINICAL PHARMACOLOGY, Pharmacodynamics: In the third paragraph, third sentence, the word "renal" should be changed to "renin."

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

If you have any questions, please contact:

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

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020184/S003

FINAL PRINTED LABELING

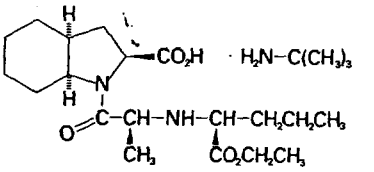
ACEON®
(perindopril erbumine) Tablets

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, ACEON should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

ACEON® (perindopril erbumine) is the tert-butylamine salt of perindopril, the ethyl ester of a non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor. Perindopril erbumine is chemically described as (2S,3aS,7aS)-1-[(S)-N-[(S)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1). Its molecular formula is $C_{19}H_{32}N_2O_5C_4H_{11}N$. Its structural formula is:



Perindopril erbumine is a white, crystalline powder with a molecular weight of 368.47 (free acid) or 441.61 (salt form). It is freely soluble in water (60% w/w), alcohol and chloroform.

Perindopril is the free acid form of perindopril erbumine, is a prodrug and metabolized *in vivo* by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite.

ACEON tablets are available in 2 mg, 4 mg and 8 mg strengths for oral administration. In addition to perindopril erbumine, each tablet contains the following inactive ingredients: colloidal silica (hydrophobic), lactose, magnesium stearate and microcrystalline cellulose. The 4 and 8 mg tablets also contain iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: ACEON (perindopril erbumine) is a prodrug for perindoprilat, which inhibits ACE in human subjects and animals. The mechanism through which perindoprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes conversion of the inactive decapeptide, angiotensin I, to the vasoconstriction, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor, which stimulates aldosterone secretion by the adrenal cortex, and provides negative feedback on renin secretion. Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and may be associated with a small increase of serum potassium.

ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ACEON remains to be elucidated.

While the principal mechanism of perindopril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect even in apparent low-renin hypertension. Perindopril has been studied in relatively few black patients, usually a low-renin population, and the average response of diastolic blood pressure to perindopril was about half the response seen in nonblacks, a finding consistent with previous experience of other ACE inhibitors.

After administration of perindopril, ACE is inhibited in a dose- and blood concentration-related fashion, with the maximal inhibition of 80 to 90% attained by 8 mg persisting for 10 to 12 hours. Twenty-four hour ACE inhibition is about 60% after these doses. The degree of ACE inhibition achieved by a given dose appears to diminish over time (the ID_{50} increases). The pressor response to an angiotensin I infusion is reduced by perindopril, but this effect is not as persistent as the effect on ACE; there is about 35% inhibition at 24 hours after a 12 mg dose.

Pharmacokinetics: Oral administration of ACEON (perindopril erbumine) 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 **PRECAUTIONS: Food Interactions.**)

ACEON®
(perindopril erbumine)
Tablets

IN-7001
Rev. 8/96

ACEON®
(perindopril
erbumine)
Tablets

Rev. 8/96

IN-7001

With 4, 8 and 16 mg doses of ACEON, C_{max} 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.

Perindopril exhibits multiexponential pharmacokinetics following oral administration. The mean half-life of perindopril associated with most of its elimination is approximately 0.8 to 1.0 hours. At very low plasma concentrations of perindopril (<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 once-daily dosing with perindopril, perindoprilat accumulates about 1.5 to 2.0 fold and attains steady-state plasma levels in 3 to 6 days. The clearance of perindoprilat and its metabolites is almost exclusively renal.

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 (<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.

Elderly Patients: Plasma concentrations of both perindopril and perindoprilat in elderly patients (>70 yrs) are approximately twice those observed in younger patients, reflecting both increased conversion of perindopril to perindoprilat and decreased renal excretion of perindoprilat. (see **PRECAUTIONS: Geriatric Use.**)

Heart Failure Patients: Perindoprilat clearance is reduced in congestive heart failure patients, resulting in a 40% higher dose interval AUC. (see **DOSAGE AND ADMINISTRATION.**)

Patients with Renal Insufficiency: With perindopril erbumine doses of 2 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 52.0 mL/min). Perindoprilat dialysis clearance ranged from 37.4 to 91.0 mL/min (mean 67.2 mL/min). (see **DOSAGE AND ADMINISTRATION.**)

Patients with Hepatic Insufficiency: The bioavailability of perindoprilat is increased in patients with impaired hepatic function. Plasma concentrations of perindoprilat in patients with impaired liver function were about 50% higher than those observed in healthy subjects or hypertensive patients with normal liver function.

Pharmacodynamics: In placebo-controlled studies of perindopril monotherapy (2 to 16 mg o.d.) in patients with mean blood pressure of about 150/100 mm Hg, 2 mg had little effect, but doses of 4 to 16 mg lowered blood pressure. The 8 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 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 B.I.D. regimen was generally slightly superior, but by not more than about 0.5 to 1 mm Hg. After 2 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 HCTZ, it had an added effect similar in magnitude to its effect as monotherapy, but 2 to 8 mg doses were approximately equal in effectiveness. In general, the effect of perindopril

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 co-administering ACEON with a calcium channel blocker, a loop diuretic or triple therapy (beta-blocker, vasodilator and a diuretic) do 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 renal angiotension system. A controlled pharmacokinetic study has shown no effect on plasma digoxin concentrations when coadministered with ACEON. (see **PRECAUTIONS: Drug Interactions.**)

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 blacks than in nonblacks. In elderly patients (≥60 years), the mean blood pressure effect was somewhat smaller than in younger patients, although the difference was not significant.

INDICATIONS AND USAGE

ACEON (perindopril erbumine) is indicated for the treatment of patients with essential hypertension. ACEON may be used alone or given with other classes of antihypertensives, especially thiazide diuretics.

When using ACEON, consideration should be given to the fact that another angiotensin converting enzyme inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to 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 nonblacks. 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 nonblacks. (see **WARNINGS: Angioedema.**)

CONTRAINDICATIONS

ACEON (perindopril erbumine) is contraindicated in patients known to be hypersensitive to this product or to any other ACE inhibitor. ACEON is also contraindicated in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

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

Angioedema: Angioedema involving the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including ACEON (perindopril erbumine) (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 mL 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.

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

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.**)

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 such 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.

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 trails of ACEON are insufficient to show whether ACEON causes agranulocytosis at similar rates.

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

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

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

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

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Perindopril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of perindopril were seen in studies of pregnant rats, mice, rabbits and cynomologous monkeys. On a mg/m^2 basis, the doses used in these studies were 6 times (in mice), 670 times (in rats), 50 times (in rabbits) and 17 times (in monkeys) the maximum recommended human dose (assuming a 50 kg adult). On a mg/kg basis, these multiples are 60 times (in mice), 3,750 times (in rats), 150 times (in rabbits) and 50 times (in monkeys) the maximum recommended human dose.

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.

PRECAUTIONS

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

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.

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 **DOSAGE AND ADMINISTRATION.**)

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 to 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 **PRECAUTIONS: Drug Interactions.**)

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

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

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with ACE inhibitor therapy, especially following the first dose. Patients should be told 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 physician.

Symptomatic Hypotension: As with any antihypertensive therapy, patients should be cautioned that lightheadedness can occur, especially during the first few days of therapy and that it should be reported promptly. Patients should be told that if fainting occurs, ACEON should be discontinued and a physician consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea or vomiting can lead to an excessive fall in blood pressure in association with ACE inhibitor therapy.

Hyperkalemia: Patients should be advised not to use potassium supplements or salt substitutes containing potassium without a physician's advice.

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

Pregnancy: Female patients of childbearing age should be told about the consequences of second and third trimester exposure

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

Drug Interactions: *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, DOSAGE AND ADMINISTRATION.**)

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.

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.

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.

Digoxin: A controlled pharmacokinetic study has shown no effect on plasma digoxin concentrations when coadministered with ACEON, but an effect of digoxin on the plasma concentration of perindopril/perindoprilat has not been excluded.

Gentamicin: Animal data have suggested the possibility of interaction between perindopril and gentamicin. However, this has not been investigated in human studies. Coadministration of both drugs should proceed with caution.

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 trails, perindopril was generally administered in a non-fasting state.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* No evidence of carcinogenic effect was observed in studies in rats and mice when perindopril was administered at dosages up to 20 times (mg/kg) or 2 to 4 times (mg/m^2) the maximum proposed clinical doses (16 mg/day) for 104 weeks.

Mutagenesis: No genotoxic potential was detected for ACEON, perindoprilat and other metabolites in various *in vitro* and *in vivo* investigations, including the Ames test, the *Saccharomyces cerevisiae* D4 test, cultured human lymphocytes, TK+/- mouse lymphoma assay, mouse and rat micronucleus tests and Chinese hamster bone marrow assay.

Impairment of Fertility: There was no meaningful effect on reproductive performance or fertility in the rat given up to 30 times (mg/kg) or 6 times (mg/m^2) the proposed maximum clinical dosage of ACEON during the period of spermatogenesis in males or oogenesis and gestation in females.

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

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.

Pediatric Use: Safety and effectiveness of ACEON in pediatric patients have not been established.

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 elderly patients compared to concentrations in younger patients. No adverse effects were clearly increased in older patients with the exception of dizziness and possibly rash. Experience with ACEON in elderly patients at daily doses exceeding 8 mg in limited.

ADVERSE REACTIONS

ACEON (perindopril erbumine) 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). 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 felt to be related to study drug) are shown 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.

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	12.0	4.5	6.0	1.8
Back Pain	5.8	3.1	0.0	0.0
Sinusitis	5.2	3.6	0.6	0.0
Viral Infection	3.4	1.6	0.3	0.0
Upper Extremity Pain	2.8	1.4	0.2	0.0
Hypertonia	2.7	1.4	0.2	0.0
Dyspepsia	1.9	0.9	0.3	0.0
Fever	1.5	0.5	0.3	0.0
Proteinuria	1.5	0.5	1.0	0.5
Ear Infection	1.3	0.0	0.0	0.0
Palpitation	1.1	0.0	0.9	0.0

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 2.0%), 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 1.0%), 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 experiences reported in 0.3 to 1% of patients in U.S. placebo-controlled studies without regard to attribution to therapy. Less frequent but medically important adverse events are also included; the incidence of these events are 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, myaliga

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).

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 pemphigus, 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.

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

Clinical Laboratory Test Findings: 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 **PRECAUTIONS.**)

BUN/Serum Creatinine Elevations: Elevations, usually transient and minor, of BUN or 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 **PRECAUTIONS.**)

Hematology: Small decreases in hemoglobin and hematocrit occur frequently in hypertensive patients treated with ACEON, but are rarely of clinical importance. In controlled clinical trials, no patient was discontinued from therapy due to the development of anemia. Leukopenia (including neutropenia) was observed in 0.1% of patients in U.S. clinical trials. (see **WARNINGS.**)

Liver Function Tests: Elevations in ALT (1.6% ACEON vs 0.9% placebo) and AST (0.5% ACEON vs 0.4% placebo) have been observed in U.S. placebo-controlled clinical trials. The elevations were generally mild and transient and resolved after discontinuation of therapy.

OVERDOSAGE

In animals, doses of perindopril up to 2500 mg/kg in mice, 3000 mg/kg in rats and 1600 mg/kg in dogs were non-lethal. Past experiences were scant, but suggested that overdosage with other ACE inhibitors was also fairly well tolerated by humans. The most likely manifestation is hypotension and treatment should be symptomatic and supportive. Therapy with the ACE inhibitor should be discontinued, and the patient should be observed. Dehydration, electrolyte imbalance and hypotension should be treated by established procedures.

However, of the reported cases of perindopril overdosage, one (dosage unknown) required assisted ventilation and the other developed hypothermia, circulatory arrest and died following ingestion of up to 180 mg of perindopril. The intervention for perindopril overdose may require vigorous support (see below).

Laboratory determinations of serum levels of perindopril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of perindopril overdose.

No data are available to suggest physiological maneuvers (*e.g.*, maneuvers to change the pH of the urine) that might accelerate elimination of perindopril and its metabolites. Perindopril can be removed by hemodialysis, with clearance of 52 mL/min for perindopril and 67 mL/min for perindoprilat.

Angiotensin II could presumably serve as a specific antagonist-antidote in the settling of perindopril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities.

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

DOSAGE AND ADMINISTRATION

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 usual maintenance dose range is 4 to 8 mg administered as a single daily dose. ACEON 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. regimen was generally slightly superior, but not by more than about 0.5 to 1.0 mm Hg.

Use in the Elderly Patients: As in younger patients, the recommended initial dosages of ACEON for the elderly (>65 years) is 4 mg daily in one or in 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 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 with 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 beginning of ACEON therapy. (see **WARNINGS.**) Then, if blood pressure is not controlled with ACEON 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, PRECAUTIONS: Drug Interactions.**)

Use in Patients with Impaired Renal Function: 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 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.

HOW SUPPLIED

Strength	Size	NDC 0075-	Color	Markings
2 mg	bottles of 100	0162-00	white and scored	162
4 mg	bottles of 100	0164-00	pink and scored	164
8 mg	bottles of 100	0168-00	salmon-colored and scored	168

Storage Conditions: Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP]. Protect from moisture.

Caution: Federal (USA) law prohibits dispensing without prescription.

ACEON® is a product of Servier Research SERVIER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

Revised 8/96 IN-7001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020184/ S003

LABELING REVIEW(S)

DF

DEC 3 1996

RHPM Review of Labeling

NDA: 20-184/SLR-003 Aceon (perindopril) Tablets

Date of submission: November 15, 1996

Date of receipt: November 21, 1996

Applicant: Rhone-Poulenc Rorer

Background: NDA 20-184 Aceon (perindopril erbumine) Tablets was approved based on draft labeling on December 30, 1993. The NDA was sold by R. W. Johnson to Amaric Corportation on March 1, 1995, and by Amaric Corporation to Rhone-Poulenc Rorer on December 22, 1995. The November 15, 1996 submission contains the first final printed labeling submitted for this product.

In addition to being reformatted to conform to the firm's labeling conventions, this labeling also includes the following changes:

Revision to the INDICATION AND USAGE section, as we requested in our January 27, 1995 supplement request letter;

Revision to the WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid reactions during membrane exposure subsection, as we requested in our March 8, 1996 facsimile;

Revision to the Pediatric Use Statement; and

Revisions requested in the CDER Stability Committee Uniform Storage Statement Memorandum.

Review:

INDICATIONS AND USAGE: Rather than using the language we suggested in our January 27, 1995 Supplement Request letter ("In considering use of Tradename, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see WARNINGS, Angioedema)." the firm has slightly revised the second sentence; the following has been added:

"In considering use of ACEON, it shold be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks. 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 nonblacks. (see WARNINGS: Angioedema.)"

WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid reactions during membrane exposure:

The phrase " (a procedure dependent upon devices not approved in the United States)" has been deleted, as we requested in our facsimile dated March 8, 1996.

PRECAUTIONS, Pediatric Use: The word "children" has been replaced with "pediatric patients" as required by the regulations on the revision of the Pediatric Use subsection of the labeling (Federal Register Notice of December 13, 1994, pgs. 64240-50).

HOW SUPPLIED: The storage conditions have been revised to comply with the CDER Stability

Committee Uniform Storage Statement. In addition, the sentence "ACEON is a product of Servier Research." has been added, and the Rhone-Poulenc Rorer signature line has been added.

I noted the following errors in the package insert that should be corrected at the time of the next printing:

CLINICAL PHARMACOLOGY, Mechanism of Action: In the first paragraph, third sentence, the word "vasoconstriction" should be changed to "vasoconstrictor."

CLINICAL PHARMACOLOGY, Pharmacodynamics: In the third paragraph, third sentence, the word "renal" should be changed to "renin."

Recommendation: I will prepare an approval letter for this supplement. This supplement falls under 21 CFR 314.70 (b)(2), Supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni

12-3-96

cc: NDA 20-184/S-003
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/12/3/96.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020184/S003

CHEMISTRY REVIEW(S)

NOV 27 1996

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-184
3. Name and Address of Applicant (City & State) Rhone-Poulenc Rorer Pharmaceuticals Inc. 500 Arcola Road P.O. Box 1200 Collegeville, PA 19426-0107		4. Supplement(s) Number(s) – Date(s) S-003 11/15/96 (LR)
5. Drug Name ACEON	6. Nonproprietary Name Perindopril Erbumine	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Final printed labeling.		
9. Pharmacological Category Antihypertensive; Angiotensin Converting Enzyme (ACE) inhibitor	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 2 mg, 4 mg, 8 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Insert - IN-7001 Rev. 8/96 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

Annotated version of the labeling submitted.

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER		
Name Danute G. Cunningham	Signature Danute G. Cunningham	Date Completed November 26, 1996

Distribution:

☐ Original Jacket ☐ Reviewer ☒ Division File ☐ CSO ☐ District

20184S03.SUP

11/27/96