

ACEON®
(perindopril erbumine) Tablets

R_x only

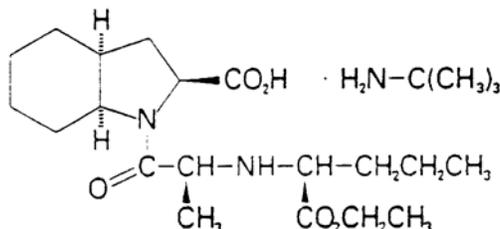
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USE IN PREGNANCY

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

DESCRIPTION

ACEON® (perindopril erbumine) Tablets is the tert-butylamine salt of perindopril, the ethyl ester of a non-sulphydryl angiotensin-converting enzyme (ACE) inhibitor. Perindopril erbumine is chemically described as (2S,3 α S,7 α S)-1-[(S)-N-[(S)-1-Carboxy-butyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1). Its molecular formula is C₁₉H₃₂N₂O₅C₄H₁₁N. 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 pro-drug and metabolized *in vivo* by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite.

ACEON® Tablets is 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) Tablets is a pro-drug 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 vasoconstrictor, 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.

39
40 ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels
41 of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ACEON®
42 Tablets remains to be elucidated.

43
44 While the principal mechanism of perindopril in blood pressure reduction is believed to be
45 through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect even in
46 apparent low-renin hypertension. Perindopril has been studied in relatively few black patients,
47 usually a low-renin population, and the average response of diastolic blood pressure to
48 perindopril was about half the response seen in nonblacks, a finding consistent with previous
49 experience of other ACE inhibitors.

50
51 After administration of perindopril, ACE is inhibited in a dose and blood concentration-
52 related fashion, with the maximal inhibition of 80 to 90% attained by 8 mg persisting for 10 to
53 12 hours. Twenty-four hour ACE inhibition is about 60% after these doses. The degree of ACE
54 inhibition achieved by a given dose appears to diminish over time (the ID₅₀ increases). The
55 pressor response to an angiotensin I infusion is reduced by perindopril, but this effect is not as
56 persistent as the effect on ACE; there is about 35% inhibition at 24 hours after a 12 mg dose.

57
58 **Pharmacokinetics:** Oral administration of ACEON® (perindopril erbumine) Tablets results in
59 its rapid absorption with peak plasma concentrations occurring at approximately 1 hour. The
60 absolute oral bioavailability of perindopril is about 75%. Following absorption, approximately
61 30 to 50% of systemically available perindopril is hydrolyzed to its active metabolite,
62 perindoprilat, which has a mean bioavailability of about 25%. Peak plasma concentrations of
63 perindoprilat are attained 3 to 7 hours after perindopril administration. The presence of food in
64 the gastrointestinal tract does not affect the rate or extent of absorption of perindopril but reduces
65 bioavailability of perindoprilat by about 35%. (See **PRECAUTIONS: Food Interaction.**)

66
67 With 4, 8 and 16 mg doses of ACEON® Tablets, C_{max} and AUC of perindopril and
68 perindoprilat increase in a linear and dose-proportional manner following both single oral dosing
69 and at steady state during a once-a-day multiple dosing regimen.

70
71 Perindopril exhibits multiexponential pharmacokinetics following oral administration. The
72 mean half-life of perindopril associated with most of its elimination is approximately 0.8 to 1
73 hours. At very low plasma concentrations of perindopril (<3 ng/mL), there is a prolonged
74 terminal elimination half-life, similar to that seen with other ACE inhibitors, that results from
75 slow dissociation of perindopril from plasma/tissue ACE binding sites. Perindopril does not
76 accumulate with a once-a-day multiple dosing regimen. Mean total body clearance of perindopril
77 is 219 to 362 mL/min and its mean renal clearance is 23.3 to 28.6 mL/min.

78
79 Perindopril is extensively metabolized following oral administration, with only 4 to 12% of
80 the dose recovered unchanged in the urine. Six metabolites resulting from hydrolysis,
81 glucuronidation and cyclization via dehydration have been identified. These include the active
82 ACE inhibitor, perindoprilat (hydrolyzed perindopril), perindopril and perindoprilat
83 glucuronides, dehydrated perindopril and the diastereoisomers of dehydrated perindoprilat. In
84 humans, hepatic esterase appears to be responsible for the hydrolysis of perindopril.

85

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

95

96 Approximately 60% of circulating perindopril is bound to plasma proteins, and only 10 to
97 20% of perindoprilat is bound. Therefore, drug interactions mediated through effects on protein
98 binding are not anticipated.

99

100 At usual antihypertensive dosages, little radioactivity (<5% of the dose) was distributed to the
101 brain after administration of ¹⁴C-perindopril to rats.

102

103 Radioactivity was detectable in fetuses and in milk after administration of ¹⁴C-perindopril to
104 pregnant and lactating rats.

105

106 **Elderly Patients:** Plasma concentrations of both perindopril and perindoprilat in elderly patients
107 (>70 yrs) are approximately twice those observed in younger patients, reflecting both increased
108 conversion of perindopril to perindoprilat and decreased renal excretion of perindoprilat. (See
109 **PRECAUTIONS: Geriatric Use.**)

110

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

113

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

118

119 In a limited number of patients studied, perindopril dialysis clearance ranged from 41.7 to
120 76.7 mL/min (mean 52 mL/min). Perindoprilat dialysis clearance ranged from 37.4 to 91 mL/min
121 (mean 67.2 mL/min). (See **DOSAGE AND ADMINISTRATION.**)

122

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

127

128 **Pharmacodynamics and Clinical Effects:**

129

130 **Stable Coronary Artery Disease**

131 The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery
 132 disease (EUROPA) was a multicenter, randomized, double-blind and placebo-controlled study
 133 conducted in 12,218 patients who had evidence of stable coronary artery disease without clinical
 134 heart failure. Patients had evidence of coronary artery disease documented by previous
 135 myocardial infarction more than 3 months before screening, coronary revascularization more
 136 than 6 months before screening, angiographic evidence of stenosis (at least 70% narrowing of
 137 one or more major coronary arteries), or positive stress test in men with a history of chest pain.
 138 After a run-in period of 4 weeks during which all patients received perindopril 2 mg to 8 mg, the
 139 patients were randomly assigned to perindopril 8 mg once daily (n=6,110) or matching placebo
 140 (n=6,108). The mean follow-up was 4.2 years. The study examined the long-term effects of
 141 perindopril on time to first event of cardiovascular mortality, nonfatal myocardial infarction, or
 142 cardiac arrest in patients with stable coronary artery disease.
 143

144 The mean age of patients was 60 years; 85% were male, 92% were taking platelet inhibitors,
 145 63% were taking β blockers, and 56% were taking lipid-lowering therapy. The EUROPA study
 146 showed that perindopril significantly reduced the relative risk for the primary endpoint events
 147 (Table 1). This beneficial effect is largely attributable to a reduction in the risk of nonfatal
 148 myocardial infarction. This beneficial effect of perindopril on the primary outcome was evident
 149 after about one year of treatment (Figure 1).
 150
 151

Table 1. Primary Endpoint and Relative Risk Reduction

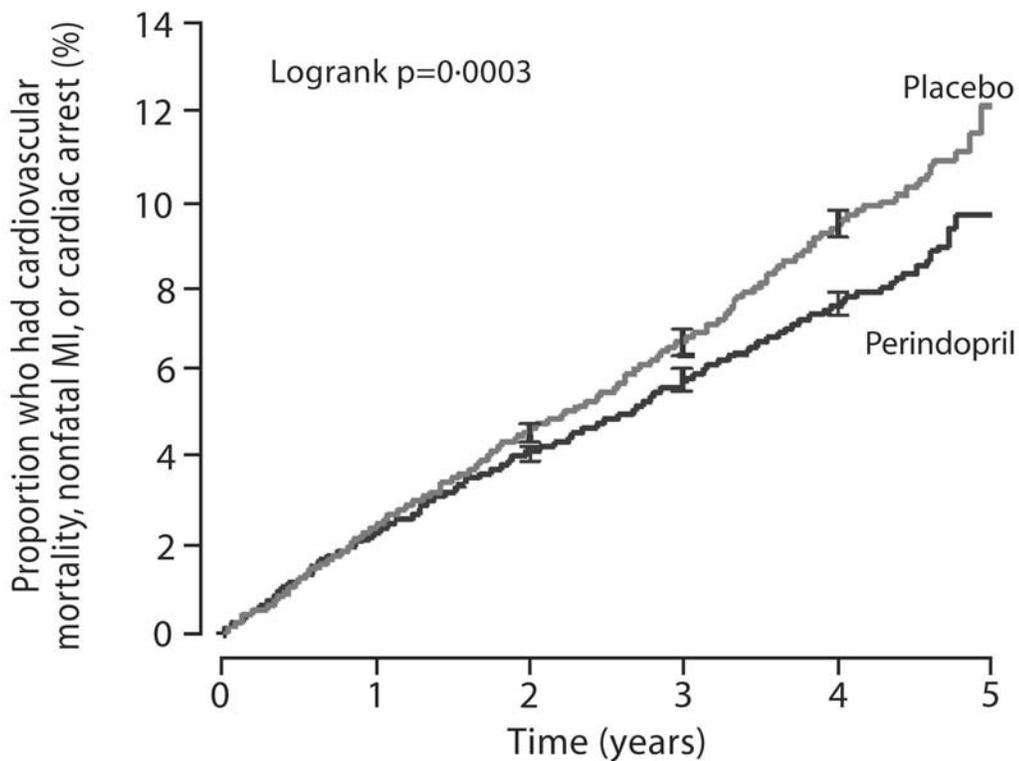
	Perindopril (N = 6,110)	Placebo (N = 6,108)	RRR (95% CI)	P
Combined Endpoint				
Cardiovascular mortality, nonfatal MI or cardiac arrest	488 (8%)	603 (9.9%)	20% (9 to 29)	0.0003
Component Endpoint				
Cardiovascular mortality	215 (3.5%)	249 (4.1%)	14% (-3 to 28)	0.107
Nonfatal MI	295 (4.8%)	378 (6.2%)	22% (10 to 33)	0.001
Cardiac arrest	6 (0.1%)	11 (0.2%)	46% (-47 to 80)	0.22

RRR: relative risk reduction; MI: myocardial infarction

152 The outcome was similar across all predefined subgroups by age, underlying disease or
 153 concomitant medication (Figure 2).
 154

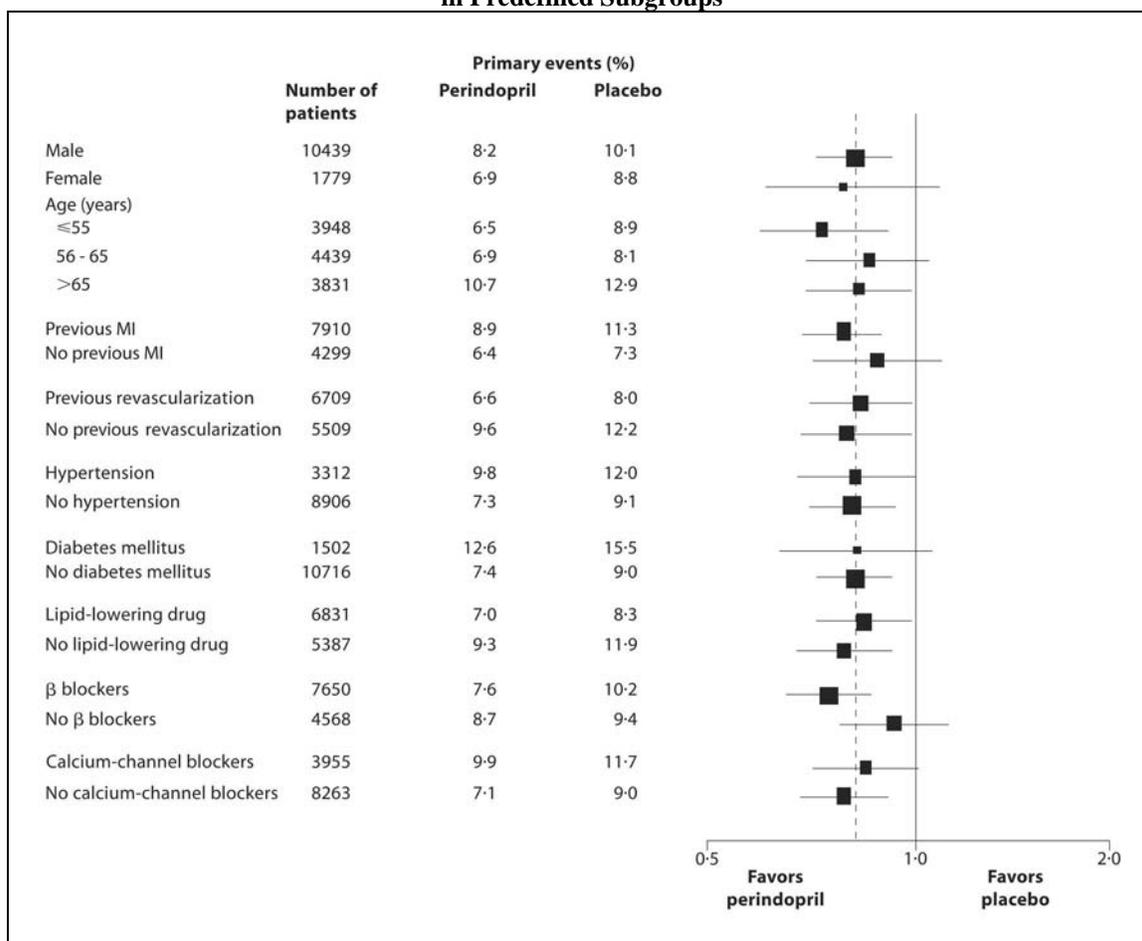
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Figure 1. Time to First Occurrence of Primary Endpoint



Patients at risk							
Placebo	6108	5943	5781	5598	4450	71	
Perindopril	6110	5957	5812	5653	4515	64	

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160**Figure 2. Beneficial Effect of Perindopril Treatment on Primary Endpoint in Predefined Subgroups**

Size of squares proportional to the number of patients in that group. Dashed line indicates overall relative risk.

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179**Hypertension**

In placebo-controlled studies of perindopril monotherapy (2 to 16 mg q.d.) in patients with a 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 occurred promptly, with effects increasing slightly over several weeks.

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

187
188 Formal interaction studies of ACEON® Tablets have not been carried out with
189 antihypertensive agents other than thiazides. Limited experience in controlled and uncontrolled
190 trials coadministering ACEON® Tablets with a calcium channel blocker, a loop diuretic or triple
191 therapy (beta-blocker, vasodilator and a diuretic), does not suggest any unexpected interactions.
192 In general, ACE inhibitors have less than additive effects when given with beta-adrenergic
193 blockers, presumably because both work in part through the renin angiotensin system. A
194 controlled pharmacokinetic study has shown no effect on plasma digoxin concentrations when
195 coadministered with ACEON® Tablets. (See **PRECAUTIONS: Drug Interactions.**)

196
197 In uncontrolled studies in patients with insulin-dependent diabetes, perindopril did not appear
198 to affect glycemic control. In long-term use, no effect on urinary protein excretion was seen in
199 these patients.

200
201 The effectiveness of ACEON® Tablets was not influenced by sex and it was less effective in
202 blacks than in nonblacks. In elderly patients (≥ 60 years), the mean blood pressure effect was
203 somewhat smaller than in younger patients, although the difference was not significant.

204

205 **INDICATIONS AND USAGE**

206

207 **Stable Coronary Artery Disease**

208 ACEON® (perindopril erbumine) Tablets is indicated in patients with stable coronary artery
209 disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction.

210 ACEON® Tablets can be used with conventional treatment for management of coronary artery
211 disease, such as antiplatelet, antihypertensive or lipid-lowering therapy.

212

213 **Hypertension**

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

217

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

222

223 In considering use of ACEON® Tablets, it should be noted that in controlled trials ACE
224 inhibitors have an effect on blood pressure that is less in black patients than in nonblacks. In
225 addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been

226 reported to have a higher incidence of angioedema compared to nonblacks. (See **WARNINGS:**
227 *Head and Neck Angioedema.*)

228

229 **CONTRAINDICATIONS**

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

234

235 **WARNINGS**

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

240

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

252

253 **Intestinal Angioedema:** Intestinal angioedema has been reported in patients treated with ACE
254 inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in
255 some cases there was no prior history of facial angioedema and C-1 esterase levels were normal.
256 The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at
257 surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should
258 be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal
259 pain.

260

261 **Anaphylactoid Reactions During Desensitization:** Two patients undergoing desensitizing
262 treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening
263 anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors
264 were temporarily withheld, but they reappeared upon inadvertent rechallenge.

265

266 **Anaphylactoid Reactions During Membrane Exposure:** Anaphylactoid reactions have been
267 reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE
268 inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density
269 lipoprotein apheresis with dextran sulfate absorption.

270

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

275
276 Symptomatic hypotension associated with the use of ACE inhibitors is more likely to occur in
277 patients who have been volume and/or salt-depleted, as a result of prolonged diuretic therapy,
278 dietary salt restriction, dialysis, diarrhea or vomiting. Volume and/or salt depletion should be
279 corrected before initiating therapy with ACEON® Tablets. (See **DOSAGE AND**
280 **ADMINISTRATION.**)

281
282 In patients with congestive heart failure, with or without associated renal insufficiency, ACE
283 inhibitors may cause excessive hypotension, and may be associated with oliguria or azotemia,
284 and rarely with acute renal failure and death. In patients with ischemic heart disease or
285 cerebrovascular disease such an excessive fall in blood pressure could result in a myocardial
286 infarction or a cerebrovascular accident.

287
288 In patients at risk of excessive hypotension, ACEON® Tablets therapy should be started
289 under very close medical supervision. Patients should be followed closely for the first two weeks
290 of treatment and whenever the dose of ACEON® Tablets and/or diuretic is increased.

291
292 If excessive hypotension occurs, the patient should be placed immediately in a supine position
293 and, if necessary, treated with an intravenous infusion of physiological saline. ACEON® Tablets
294 treatment can usually be continued following restoration of volume and blood pressure.

295
296 **Neutropenia/Agranulocytosis:** Another ACE inhibitor, captopril, has been shown to cause
297 agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more
298 frequently in patients with renal impairment, especially patients with a collagen vascular disease
299 such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of
300 ACEON® Tablets are insufficient to show whether ACEON® Tablets causes agranulocytosis at
301 similar rates.

302
303 **Fetal/Neonatal Morbidity and Mortality:** ACE inhibitors can cause fetal and neonatal
304 morbidity and death when administered to pregnant women. Several dozen cases have been
305 reported in the world literature. When pregnancy is detected, ACE inhibitors should be
306 discontinued as soon as possible.

307
308 **The use of ACE inhibitors during the second and third trimesters of pregnancy** has been
309 associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia,
310 anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported,
311 presumably resulting from decreased fetal renal function; oligohydramnios in this setting has
312 been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung
313 development.

314

315 Prematurity, intrauterine growth retardation, patent ductus arteriosus, and other structural
316 cardiac malformations, as well as neurological malformations, have been reported following
317 exposure to ACE inhibitors during the first trimester of pregnancy.

318
319
320 When patients become pregnant, physicians should make every effort to discontinue the use of
321 ACEON® Tablets as soon as possible. Rarely (probably less often than once in every thousand
322 pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers
323 should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations
324 should be performed to assess the intra-amniotic environment.

325
326 If oligohydramnios is observed, ACEON® Tablets should be discontinued unless it is
327 considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST) or
328 biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients
329 and physicians should be aware, however, that oligohydramnios may not appear until after the
330 fetus has sustained irreversible injury.

331
332 Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for
333 hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward
334 support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required
335 as a means of reversing hypotension and/or substituting for disordered renal function.
336 Perindopril, which crosses the placenta, can theoretically be removed from the neonatal
337 circulation by these means, but limited experience has not shown that such removal is central to
338 the treatment of these infants.

339
340 No teratogenic effects of perindopril were seen in studies of pregnant rats, mice, rabbits and
341 cynomolgus monkeys. On a mg/m² basis, the doses used in these studies were 6 times (in mice),
342 670 times (in rats), 50 times (in rabbits) and 17 times (in monkeys) the maximum recommended
343 human dose (assuming a 50 kg adult). On a mg/kg basis, these multiples are 60 times (in mice),
344 3,750 times (in rats), 150 times (in rabbits) and 50 times (in monkeys) the maximum
345 recommended human dose.

346
347 **Hepatic Failure:** Rarely, ACE inhibitors have been associated with a syndrome that starts with
348 cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The
349 mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop
350 jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and
351 receive appropriate medical follow-up.

352 353 **PRECAUTIONS**

354 **General:**

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

357
358 **Hypertensive Patients with Congestive Heart Failure:** In patients with severe congestive heart
359 failure, where renal function may depend on the activity of the renin-angiotensin-aldosterone

360 system, treatment with ACE inhibitors, including ACEON® Tablets, may be associated with
361 oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death.

362
363 **Hypertensive Patients with Renal Artery Stenosis:** In hypertensive patients with unilateral or
364 bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur.
365 Experience with ACE inhibitors suggests that these increases are usually reversible upon
366 discontinuation of the drug. In such patients, renal function should be monitored during the first
367 few weeks of therapy.

368
369 Some hypertensive patients without apparent pre-existing renal vascular disease have
370 developed increases in blood urea nitrogen and serum creatinine, usually minor and transient.
371 These increases are more likely to occur in patients treated concomitantly with a diuretic and in
372 patients with pre-existing renal impairment. Reduction of dosages of ACEON® Tablets, the
373 diuretic or both may be required. In some cases, discontinuation of either or both drugs may be
374 necessary.

375
376 Evaluation of hypertensive patients should always include an assessment of renal function.
377 (See **DOSAGE AND ADMINISTRATION.**)

378
379 **Hyperkalemia:** Elevations of serum potassium have been observed in some patients treated with
380 ACE inhibitors, including ACEON® Tablets. In U.S. controlled clinical trials, 1.4% of the
381 patients receiving ACEON® Tablets and 2.3% of patients receiving placebo showed increased
382 serum potassium levels to greater than 5.7 mEq/L. Most cases were isolated single values that
383 did not appear clinically relevant and were rarely a cause for withdrawal. Risk factors for the
384 development of hyperkalemia include renal insufficiency, diabetes mellitus and the concomitant
385 use of agents such as potassium-sparing diuretics, potassium supplements and/or potassium-
386 containing salt substitutes. Drugs associated with increases in serum potassium should be used
387 cautiously, if at all, with ACEON® Tablets. (See **PRECAUTIONS: Drug Interactions.**)

388
389 **Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent
390 nonproductive cough has been reported with all ACE inhibitors, always resolving after
391 discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential
392 diagnosis of cough. In controlled trials with perindopril, cough was present in 12% of perindopril
393 patients and 4.5% of patients given placebo.

394
395 **Surgery/Anesthesia:** In patients undergoing surgery or during anesthesia with agents that
396 produce hypotension, ACEON® Tablets may block angiotensin II formation that would
397 otherwise occur secondary to compensatory renin release. Hypotension attributable to this
398 mechanism can be corrected by volume expansion.

399
400 **Information for Patients:**

401 **Angioedema:** Angioedema, including laryngeal edema, can occur with ACE inhibitor therapy,
402 especially following the first dose. Patients should be told to report immediately signs or
403 symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, hoarseness or
404 difficulty in swallowing or breathing) and to take no more drug before consulting a physician.

405

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

410
411 All patients should be cautioned that inadequate fluid intake or excessive perspiration,
412 diarrhea or vomiting can lead to an excessive fall in blood pressure in association with ACE
413 inhibitor therapy.

414
415 **Hyperkalemia:** Patients should be advised not to use potassium supplements or salt substitutes
416 containing potassium without a physician's advice.

417
418 **Neutropenia:** Patients should be told to report promptly any indication of infection (*e.g.*, sore
419 throat, fever) which could be a sign of neutropenia.

420
421 **Pregnancy:** Female patients of childbearing age should be told about the consequences of
422 exposure to ACE inhibitors during pregnancy. Discuss other treatment options with women
423 planning to become pregnant. Women who do become pregnant while on an ACE inhibitor
424 (including ACEON®) should be asked to stop the medication and contact their physician as soon
425 as possible.

426
427 **Drug Interactions:**

428 **Diuretics:** Patients on diuretics, and especially those started recently, may occasionally
429 experience an excessive reduction of blood pressure after initiation of ACEON® Tablets therapy.
430 The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or
431 increasing the salt intake prior to initiation of treatment with perindopril. If diuretics cannot be
432 interrupted, close medical supervision should be provided with the first dose of ACEON®
433 Tablets, for at least two hours and until blood pressure has stabilized for another hour. (See
434 **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

435
436 The rate and extent of perindopril absorption and elimination are not affected by concomitant
437 diuretics. The bioavailability of perindoprilat was reduced by diuretics, however, and this was
438 associated with a decrease in plasma ACE inhibition.

439
440 **Potassium Supplements and Potassium-Sparing Diuretics:** ACEON® Tablets may increase
441 serum potassium because of its potential to decrease aldosterone production. Use of potassium-
442 sparing diuretics (spironolactone, amiloride, triamterene and others), potassium supplements or
443 other drugs capable of increasing serum potassium (indomethacin, heparin, cyclosporine and
444 others) can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is
445 indicated, they should be given with caution and the patient's serum potassium should be
446 monitored frequently.

447
448 **Lithium:** Increased serum lithium and symptoms of lithium toxicity have been reported in
449 patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be
450 coadministered with caution and frequent monitoring of serum lithium concentration is
451 recommended. Use of a diuretic may further increase the risk of lithium toxicity.

452
453 **Gold:** Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension)
454 have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate)
455 and concomitant ACE Inhibitor therapy including ACEON®.

456
457 **Digoxin:** A controlled pharmacokinetic study has shown no effect on plasma digoxin
458 concentrations when coadministered with ACEON® Tablets, but an effect of digoxin on the
459 plasma concentration of perindopril/perindoprilat has not been excluded.

460
461 **Gentamicin:** Animal data have suggested the possibility of interaction between perindopril and
462 gentamicin. However, this has not been investigated in human studies. Coadministration of both
463 drugs should proceed with caution.

464
465
466 **Food Interaction:** Oral administration of ACEON® Tablets with food does not significantly
467 lower the rate or extent of perindopril absorption relative to the fasted state. However, the extent
468 of biotransformation of perindopril to the active metabolite, perindoprilat, is reduced
469 approximately 43%, resulting in a reduction in the plasma ACE inhibition curve of
470 approximately 20%, probably clinically insignificant. In clinical trials, perindopril was generally
471 administered in a non-fasting state.

472
473 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

474 **Carcinogenesis:** No evidence of carcinogenic effect was observed in studies in rats and mice
475 when perindopril was administered at dosages up to 20 times (mg/kg) or 2 to 4 times (mg/m²) the
476 maximum proposed clinical doses (16 mg/day) for 104 weeks.

477
478 **Mutagenesis:** No genotoxic potential was detected for ACEON® Tablets, perindoprilat and
479 other metabolites in various *in vitro* and *in vivo* investigations, including the Ames test, the
480 *Saccharomyces cerevisiae* D4 test, cultured human lymphocytes, TK ± mouse lymphoma assay,
481 mouse and rat micronucleus tests and Chinese hamster bone marrow assay.

482
483 **Impairment of Fertility:** There was no meaningful effect on reproductive performance or
484 fertility in the rat given up to 30 times (mg/kg) or 6 times (mg/m²) the proposed maximum
485 clinical dosage of ACEON® Tablets during the period of spermatogenesis in males or oogenesis
486 and gestation in females.

487
488 **Pregnancy:** Pregnancy Category D. (See **WARNINGS: Fetal/Neonatal Morbidity and**
489 **Mortality.**)

490
491 **Nursing Mothers:** Milk of lactating rats contained radioactivity following administration ¹⁴C-
492 perindopril. It is not known whether perindopril is secreted in human milk. Because many drugs
493 are secreted in human milk, caution should be exercised when ACEON® Tablets is given to
494 nursing mothers.

495
496 **Pediatric Use:** Safety and effectiveness of ACEON® Tablets in pediatric patients have not been
497 established.

498
 499 **Geriatric Use:** The mean blood pressure effect of perindopril was somewhat smaller in patients
 500 over 60 than in younger patients, although the difference was not significant. Plasma
 501 concentrations of both perindopril and perindoprilat were increased in elderly patients compared
 502 to concentrations in younger patients. No adverse effects were clearly increased in older patients
 503 with the exception of dizziness and possibly rash.

504
 505 Perindopril should be used with caution when administered to elderly patients who are at an
 506 increased risk for falls due to age, their underlying disease and/or their concurrent use of
 507 medications(s) associated with falls. Falls and fall-related events may be exacerbated by the
 508 central nervous system effects of dizziness and syncope as well as the symptomatic hypotension,
 509 including orthostatic, associated with perindopril. Experience with ACEON® Tablets in elderly
 510 patients at daily doses exceeding 8 mg is limited.

511 **ADVERSE REACTIONS**

514 **Hypertension**

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

520
 521 The data presented here are based on results from the 1,417 ACEON® Tablets-treated
 522 patients who participated in the U.S. clinical trials. Over 220 of these patients were treated with
 523 ACEON® Tablets for at least one year.

524
 525 In placebo-controlled U.S. clinical trials, the incidence of premature discontinuation of
 526 therapy due to adverse events was 6.5% in patients treated with ACEON® Tablets and 6.7% in
 527 patients treated with placebo. The most common causes were cough, headache, asthenia and
 528 dizziness.

529
 530 Among 1,012 patients in placebo-controlled U.S. trials, the overall frequency of reported
 531 adverse events was similar in patients treated with ACEON® Tablets and in those treated with
 532 placebo (approximately 75% in each group). Adverse events that occurred in 1% or greater of the
 533 patients and that were more common for perindopril than placebo by at least 1% (regardless of
 534 whether they were felt to be related to study drug) are shown in the first two columns below. Of
 535 these adverse events, those considered possibly or probably related to study drug are shown in
 536 the last two columns.

537
 538 **Table 2.**
 539 **Frequency of Adverse Events (%)**

All Adverse Events		Possibly– or Probably– Related Adverse Events	
Perindopril	Placebo	Perindopril	Placebo

540

	n=789	n=223	n=789	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

541
542 Of these, cough was the reason for withdrawal in 1.3% of perindopril and 0.4% of placebo
543 patients. While dizziness was not reported more frequently in the perindopril group (8.2%) than
544 in the placebo group (8.5%), it was clearly increased with dose, suggesting a causal relationship
545 with perindopril. Other commonly reported complaints (1% or greater), regardless of causality,
546 include: headache (23.8%), upper respiratory infection (8.6%), asthenia (7.9%), rhinitis (4.8%),
547 low extremity pain (4.7%), diarrhea (4.3%), edema (3.9%), pharyngitis (3.3%), urinary tract
548 infection (2.8%), abdominal pain (2.7%), sleep disorder (2.5%), chest pain (2.4%), injury,
549 paresthesia, nausea, rash (each 2.3%), seasonal allergy, depression (each 2%), abnormal ECG
550 (1.8%), ALT increase (1.7%), tinnitus, vomiting (each 1.5%), neck pain, male sexual dysfunction
551 (each 1.4%), triglyceride increase, somnolence (each 1.3%), joint pain, nervousness, myalgia,
552 menstrual disorder (each 1.1%), flatulence and arthritis (each 1%), but none of those was more
553 frequent by at least 1% on perindopril than on placebo. Depending on the specific adverse event,
554 approximately 30 to 70% of the common complaints were considered possibly or probably
555 related to treatment.

556
557 **Stable Coronary Artery Disease**
558 Perindopril has been evaluated for safety in EUROPA, a double-blind, placebo-controlled study
559 in 12,218 patients with stable coronary artery disease. The overall rate of discontinuation was
560 about 22% on drug and placebo. The most common medical reasons for discontinuation that
561 were more frequent on perindopril than placebo were cough, drug intolerance and hypotension.
562

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

567
568 **Body as a Whole:** malaise, pain, cold/hot sensation, chills, fluid retention, orthostatic symptoms,
569 anaphylactic reaction, facial edema, angioedema (0.1%).

570
571 **Gastrointestinal:** constipation, dry mouth, dry mucous membrane, appetite increased,
572 gastroenteritis.
573

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

576
577 **Urogenital:** vaginitis, kidney stone, flank pain, urinary frequency, urinary retention.

578
579 **Cardiovascular:** hypotension, ventricular extrasystole, myocardial infarction, vasodilation,
580 syncope, abnormal conduction, heart murmur, orthostatic hypotension.

581
582 **Endocrine:** gout.

583
584 **Hematology:** hematoma, ecchymosis.

585
586 **Musculoskeletal:** arthralgia, myalgia.

587
588 **CNS:** migraine, amnesia, vertigo, cerebral vascular accident (0.2%).

589
590 **Psychiatric:** anxiety, psychosexual disorder.

591
592 **Dermatology:** sweating, skin infection, tinea, pruritus, dry skin, erythema, fever blisters, purpura
593 (0.1%).

594
595 **Special Senses:** conjunctivitis, earache.

596
597 **Laboratory:** potassium decrease, uric acid increase, alkaline phosphatase increase, cholesterol
598 increase, AST increase, creatinine increase, hematuria, glucose increase.

599
600 When ACEON® Tablets was given concomitantly with thiazide diuretics, adverse events
601 were generally reported at the same rate as those for ACEON® Tablets alone, except for a higher
602 incidence of abnormal laboratory findings known to be related to treatment with thiazide
603 diuretics alone (*e.g.*, increases in serum uric acid, triglycerides and cholesterol and decreases in
604 serum potassium).

605
606 **Potential Adverse Effects Reported with ACE Inhibitors:** Other medically important adverse
607 effects reported with other available ACE inhibitors include: cardiac arrest, eosinophilic
608 pneumonitis, neutropenia/agranulocytosis, pancytopenia, anemia (including hemolytic and
609 aplastic), thrombocytopenia, acute renal failure, nephritis, hepatic failure, jaundice
610 (hepatocellular or cholestatic), symptomatic hyponatremia, bullous pemphigoid, pemphigus,
611 acute pancreatitis, falls, psoriasis, exfoliative dermatitis and a syndrome which may include:
612 arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermatologic manifestations,
613 a positive ANA, leukocytosis, eosinophilia or an elevated ESR. Many of these adverse effects
614 have also been reported for perindopril.

615
616 **Fetal/Neonatal Morbidity and Mortality:** See **WARNINGS: Fetal/Neonatal Morbidity and**
617 **Mortality.**

618
619 **Clinical Laboratory Test Findings**

620 **Hypertension**

621 Hematology, clinical chemistry and urinalysis parameters have been evaluated in U.S. placebo-
622 controlled trials. In general, there were no clinically significant trends in laboratory test findings.

623

624 **Hyperkalemia:** In clinical trials, 1.4% of the patients receiving ACEON® Tablets and 2.3% of
625 the patients receiving placebo showed serum potassium levels greater than 5.7 mEq/L. (See

626 **PRECAUTIONS.**)

627

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

634

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

640

641 **Liver Function Tests:** Elevations in ALT (1.6% ACEON® Tablets vs 0.9% placebo) and AST
642 (0.5% ACEON® Tablets vs 0.4% placebo) have been observed in U.S. placebo-controlled
643 clinical trials. The elevations were generally mild and transient and resolved after
644 discontinuation of therapy.

645

646 **OVERDOSAGE**

647 In animals, doses of perindopril up to 2,500 mg/kg in mice, 3,000 mg/kg in rats and 1,600 mg/kg
648 in dogs were non-lethal. Past experiences were scant but suggested that overdosage with other
649 ACE inhibitors was also fairly well tolerated by humans. The most likely manifestation is
650 hypotension, and treatment should be symptomatic and supportive. Therapy with the ACE
651 inhibitor should be discontinued, and the patient should be observed. Dehydration, electrolyte
652 imbalance and hypotension should be treated by established procedures.

653

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

658

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

662

663 No data are available to suggest physiological maneuvers (*e.g.*, maneuvers to change the pH
664 of the urine) that might accelerate elimination of perindopril and its metabolites. Perindopril can

665 be removed by hemodialysis, with clearance of 52 mL/min for perindopril and 67 mL/min for
666 perindoprilat.

667
668 Angiotensin II could presumably serve as a specific antagonist-antidote in the settling of
669 perindopril overdose, but angiotensin II is essentially unavailable outside of scattered research
670 facilities. Because the hypotensive effect of perindopril is achieved through vasodilation and
671 effective hypovolemia, it is reasonable to treat perindopril overdose by infusion of normal saline
672 solution.

673

674 **DOSAGE AND ADMINISTRATION**

675

676 **Stable Coronary Artery Disease**

677 In patients with stable coronary artery disease, ACEON® Tablets should be given at an initial
678 dose of 4 mg once daily for 2 weeks, and then increased as tolerated, to a maintenance dose of 8
679 mg once daily. In elderly patients (>70 yrs), ACEON® Tablets should be given as a 2 mg dose
680 once daily in the first week, followed by 4 mg once daily in the second week and 8 mg once
681 daily for maintenance dose if tolerated.

682

683 **Hypertension**

684 **Use in Uncomplicated Hypertensive Patients:** In patients with essential hypertension, the
685 recommended initial dose is 4 mg once a day. The dosage may be titrated upward until blood
686 pressure, when measured just before the next dose, is controlled or to a maximum of 16 mg per
687 day. The usual maintenance dose range is 4 to 8 mg administered as a single daily dose.
688 ACEON® Tablets may also be administered in two divided doses. When once-daily dosing was
689 compared to twice-daily dosing in clinical studies, the B.I.D. regimen was generally slightly
690 superior, but not by more than about 0.5 to 1 mm Hg.

691

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

698

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

705

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

710

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

719

720 **Dose Adjustment in Renal Impairment**

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

728

729 **HOW SUPPLIED**

730 **Tablets 2 mg:** Scored one side, white, oblong (debossed “ACN 2” on one side and debossed
 731 with “SLV” on both sides of score on the other side)

732 Bottles of 100 NDC 0032-1101-01

733

734 **Tablets 4 mg:** Scored one side, pink, oblong (debossed “ACN 4” on one side and debossed
 735 with “SLV” on both sides of score on the other side)

736 Bottles of 100 NDC 0032-1102-01

737

738 **Tablets 8 mg:** Scored one side, salmon-colored, oblong (debossed “ACN 8” on one side and
 739 debossed with “SLV” on both sides of score on the other side)

740 Bottles of 100 NDC 0032-1103-01

741

742 **Storage Conditions:** Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].
 743 Protect from moisture.

744

745 **Keep out of the reach of children.**

746

747 **Manufactured by:**

748 Patheon Pharmaceuticals, Inc.

749 Cincinnati, OH 45237 USA

750

751 **Marketed by:**

752 **Solvay Pharmaceuticals, Inc.**

753 **Marietta, GA 30062**

754

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756

