

PROPOSED PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAMES (AND DOSAGE FORMS):

ACCUPRIL[®] 5 mg (tablet)

ACCUPRIL[®] 10 mg (tablet)

ACCUPRIL[®] 20 mg (tablet)

ACCUPRIL[®] 40 mg (tablet)

COMPOSITION:

ACCUPRIL 5 mg: Each tablet contains quinapril hydrochloride equivalent to 5 mg quinapril.

ACCUPRIL 10 mg: Each tablet contains quinapril hydrochloride equivalent to 10 mg quinapril.

ACCUPRIL 20 mg: Each tablet contains quinapril hydrochloride equivalent to 20 mg quinapril.

ACCUPRIL 40 mg: Each tablet contains quinapril hydrochloride equivalent to 40 mg quinapril.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines - other hypotensives

PHARMACOLOGICAL ACTION:

Quinapril hydrochloride is the hydrochloride salt of quinapril, the ethyl ester of a long-acting nonsulfhydryl, specific angiotensin-converting enzyme (ACE) inhibitor.

Quinapril is rapidly deesterified to quinaprilat (quinapril diacid, the principal metabolite) which, in human and animal studies, is an angiotensin-converting enzyme inhibitor. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II which is involved in

vascular control and function through many different mechanisms, including stimulation of aldosterone secretion by the adrenal cortex. The primary mode of action of quinapril in humans and animals is to inhibit ACE, thereby decreasing vasopressor activity and aldosterone secretion. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Quinapril has antihypertensive activity in the presence of low to normal plasma renin concentrations.

Other possible mechanisms contributing to the activity of ACE-inhibitors include bradykinin-induced vasodilation, release of prostaglandins, attenuation of sympathetic nervous system activity, and inhibition of tissue enzyme-converting activity. ACE, also known as kininase II, is the enzyme that degrades bradykinin, a potent vasodepressor peptide.

Pharmacokinetic properties and Metabolism:

Following oral administration, peak plasma quinapril concentrations are observed within one hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is approximately 60%. Quinapril absorption is not influenced by food. Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat, a potent ACE-inhibitor, and to minor inactive metabolites. Quinapril has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations are observed approximately two hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an elimination half-life of three hours, and a terminal half-life of approximately 25 hours. The excretion of quinapril and quinaprilat in patients with renal insufficiency is decreased. The elimination of quinaprilat is reduced in elderly patients (> 65 years) and correlates well with the impaired renal function which occurs in the elderly (see DOSAGE AND DIRECTIONS FOR USE). Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

Pharmacodynamic properties:

Quinapril reduces peripheral vascular resistance, mean arterial pressure, systolic and diastolic blood pressure.

INDICATIONS:

Hypertension:

ACCUPRIL is indicated for the treatment of mild to moderate hypertension. ACCUPRIL is effective as monotherapy or concomitantly with diuretics in patients with hypertension.

Congestive Heart Failure:

ACCUPRIL is indicated for the treatment of unresponsive systolic left ventricular failure of various aetiologies in which afterload reduction is advocated.

CONTRA-INDICATIONS:

ACCUPRIL is contraindicated:

- in patients who are hypersensitive to any component of this product
- patients with a history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Moderate to severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis

- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
- Porphyria

Thiazide diuretics in (fixed dose) combination with ACCUPRIL should not be given to patients with Addison's disease. This therapy is also contra-indicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines

- Lithium therapy: Concomitant administration with ACCUPRIL may lead to toxic blood concentrations of lithium
- Pregnancy and Lactation (see PREGNANCY AND LACTATION)

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped promptly and switched to a different class of medicine.

Should a woman receiving an ACE-inhibitor, contemplate pregnancy, the doctor must consider alternative medication.

ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester.

Cases of defective skull ossification have been observed.

Prematurity and low birth mass can occur (see PREGNANCY AND LACTATION).

Head and Neck Angioedema: Angioedema, including laryngeal edema, may occur, especially following the first dose of ACCUPRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to discontinue medication until they have consulted with their physician.

If laryngeal stridor or angioedema of the face, tongue, or glottis occur, treatment with ACCUPRIL should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy e.g., subcutaneous adrenalin solution 1:1000 (0,3 to 0,5 ml) should be promptly administered.

Black patients receiving ACE-inhibitor therapy have been reported to have a higher incidence of angioedema compared to non-black patients.

Intestinal Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

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:

Desensitization: Patients receiving ACE-inhibitors during desensitizing treatment with hymenoptera venom have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions

have been avoided when ACE-inhibitors were temporarily withheld, but they have reappeared upon inadvertent rechallenge.

Haemodialysis: Clinical evidence has shown that patients haemodialysed using certain high-flux membranes (such as polyacrylonitrile membranes) are likely to experience anaphylactoid reactions with concomitant ACE-inhibitor treatment. This combination should be avoided, either by use of alternative antihypertensive drugs, or alternative membranes for haemodialysis.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of ACCUPRIL therapy. If actual syncope occurs, the patients should be told to discontinue medication until they have consulted with their physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhoea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

In patients with congestive heart failure where diastolic dysfunction of the left ventricle exists, cardiac failure may be aggravated.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or any concomitant diuretic therapy should be considered if this event occurs.

Neutropenia/Agranulocytosis: ACE-inhibitors have been associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension. Agranulocytosis has been rarely reported during treatment with ACCUPRIL. Monitoring of white blood cell counts especially in patients with collagen vascular disease and/or renal disease should be considered.

Patients should be told to report promptly any indication of infection (e.g. sore throat, fever) which does not resolve within two days.

Hypoglycaemia and Diabetes: ACE-inhibitors have been associated with hypoglycaemia in diabetic patients on insulin or oral hypoglycaemic agents; closer monitoring of diabetic patients may be required.

Hyperkalaemia and potassium-sparing diuretics: Patients on ACCUPRIL alone may have increased serum potassium levels. This effect may help to reduce the hypokalaemia induced by thiazide diuretics. ACCUPRIL has not been studied as concomitant therapy with potassium-sparing diuretics. Because of the risk of further potentiating increases in serum potassium it is advised that if such combination therapy is indicated, it be initiated with caution and the patient's serum potassium levels be closely monitored. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Impaired renal function: In patients with a creatinine clearance of < 40 ml/min, the half-life of quinaprilat is prolonged. These patients should commence therapy at the lowest recommended daily dose and be titrated upwards based upon response. Renal function should be closely monitored, although initial studies in small numbers of patients do not indicate that ACCUPRIL produces further deterioration in renal function.

Use in Elderly: Elderly patients exhibited increased AUC and peak levels for quinaprilat compared to values in younger patients; this appeared to be related to decreased renal function rather than age itself. No overall differences in effectiveness or safety were observed between older and younger patients, however, greater sensitivity of some older individuals cannot be ruled out.

Surgery/Anaesthesia: Caution should be exercised when patients undergo anaesthesia since angiotensin converting enzyme inhibitors have been shown to block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

Effects on Ability to Drive and Use Machines:

The ability to engage in activities such as operating machinery or operating a motor vehicle may be impaired, especially when initiating ACCUPRIL therapy.

INTERACTIONS:

Tetracycline: Concomitant administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline in healthy volunteers because of the presence of magnesium carbonate in the formulation.

It is recommended that concomitant administration of ACCUPRIL and tetracycline be avoided.

Other Agents: No important pharmacokinetic interactions occurred when ACCUPRIL was used concomitantly with propranolol, hydrochlorothiazide, digoxin, or cimetidine.

No change in prothrombin time occurred when ACCUPRIL and warfarin were given together.

Concomitant Diuretic Therapy: Patients on diuretics, especially those on recently instituted diuretic therapy, may experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. Hypotensive effects after the first dose of ACCUPRIL may be minimized by discontinuing the diuretic a few days prior to initiation of therapy. In patients in whom a diuretic is continued, medical supervision should be provided up to two hours after the initial dosage of ACCUPRIL.

PREGNANCY AND LACTATION:

Pregnancy: There are no adequate and well-controlled studies in pregnant women. ACCUPRIL is contra-indicated throughout pregnancy. (See WARNINGS AND SPECIAL PRECAUTIONS).

Nursing mothers: Quinapril and its metabolites are secreted in human milk.

DOSAGE AND DIRECTIONS FOR USE:

ACCUPRIL may be administered without regard to meals.

Hypertension:

Monotherapy: The recommended initial dosage of ACCUPRIL in patients not on diuretics is 10 mg once daily. Depending upon clinical response, patient's dosage may be titrated (by doubling the dose) to a maintenance dosage of 20 to 40 mg/day given as a single dose or divided into two doses. Generally, dosage adjustments should be made at intervals of four weeks or according to patient's response. Long-term control is maintained in most patients with a single daily dosage regimen.

Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients.

Concomitant Diuretics: In patients who are also being treated with a diuretic, the initial dosage of ACCUPRIL is 5 mg in order to determine if excess hypotension will occur. The dosage should subsequently be titrated (as described above) to the optimal response (see WARNINGS AND SPECIAL PRECAUTIONS).

Congestive Heart Failure:

The recommended initial dosage in patients with congestive heart failure due to unresponsive systolic left ventricular failure of various aetiologies in which afterload reduction is advocated, is a single 5 mg dose, following which the patient should be monitored closely for symptomatic hypotension. Patients may be titrated up to 40 mg per day given in two doses with concomitant diuretic and/or cardiac glycoside therapy. Patients can, however, normally be maintained effectively on doses of 10 to 20 mg per day given in one or two doses with concomitant therapy.

Impaired renal function:

Patients should commence therapy at the lowest recommended daily dose and be titrated upwards based upon response. (See WARNINGS AND SPECIAL PRECAUTIONS)

Use in Elderly Patients:

In elderly patients initial therapy is 5 mg once daily followed by titration to the optimal response.

Use in Children:

The safety and effectiveness of ACCUPRIL in children has not been established.

SIDE-EFFECTS:

The adverse events reported have been categorized utilizing the incidence rate as follows:

Very common: $\geq 1/10$ ($\geq 10\%$); Common: $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$); Uncommon: $\geq 1/1\ 000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$); Rare: $\geq 1/10\ 000$ and $< 1/1\ 000$ ($\geq 0.01\%$ and $< 0.1\%$); Very Rare: $< 1/10\ 000$ ($< 0.01\%$)

MeDRA System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	Rare	Agranulocytosis, haemolytic anemia, neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylactoid reaction
Metabolism and nutrition system disorders	Common	Hyperkalaemia
Psychiatric disorders	Common	Insomnia
	Uncommon	Depression, nervousness
Nervous system disorders	Common	Dizziness, headache, paraesthesia
	Uncommon	Somnolence, vertigo
Eye disorders	Uncommon	Amblyopia
Cardiac disorders	Uncommon	Angina pectoris, palpitations, tachycardia
Vascular disorders	Common	Hypotension
	Uncommon	Vasodilation

	Rare	Postural hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Common	Cough, dyspnoea, pharyngitis, rhinitis
	Rare	Eosinophilic pneumonitis
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
	Uncommon	Dry mouth or throat, flatulence, pancreatitis
Hepatobiliary disorders	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Uncommon	Angioedema, increased perspiration, pruritus, rash
	Rare	Alopecia, exfoliative dermatitis, pemphigus, photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Back pain, myalgia
	Uncommon	Arthralgia
Renal and urinary disorders	Uncommon	Urinary tract infection
Reproductive system and breast disorders	Uncommon	Impotence

General disorders and administration site conditions	Common Uncommon	Chest pain, fatigue Oedema (peripheral and generalized)
Investigations	Common	Increased serum creatinine, increased blood urea nitrogen

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No data are available with respect to overdosage in humans. The oral LD50 of quinapril in mice and rats ranges from 1440 to 4280 mg/kg. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion.

Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

IDENTIFICATION:

ACCUPRIL 5 mg: A reddish-brown, oval, biconvex film-coated tablet with bisecting score on both sides and debossing “5” on both sides in opposite directions.

ACCUPRIL 10 mg: A reddish-brown, triangular, biconvex film-coated tablet with bisecting score on both sides and embossing “10” on one side.

ACCUPRIL 20 mg: A reddish-brown, round, biconvex, film-coated tablet, with bisecting score on both sides and debossing “20” on one side.

ACCUPRIL 40 mg: A reddish-brown, oval, biconvex, film-coated tablet, embossed “40” on one side; and “PD 535” on the other

PRESENTATION:

Blister packs of 28, 30, 60 and 90 tablets.

STORAGE INSTRUCTIONS:

Store in a cool (below 25 °C), dry place. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ACCUPRIL 5 mg: W/7.1.3/361

ACCUPRIL 10 mg: W/7.1.3/362

ACCUPRIL 20 mg: W/7.1.3/363

ACCUPRIL 40 mg: W/7.1.3/364

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Limited

85 Bute Lane

Sandton

2196

SOUTH AFRICA

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Last Council Approval: 23 July 2010

~~BOTSWANA: S2~~

~~ACCUPRIL 5 mg Reg. No.: BOT0700936~~

~~ACCUPRIL 10 mg Reg. No.: BOT0700935~~

~~ACCUPRIL 20 mg Reg. No.: BOT0700937~~

~~NAMIBIA: S2~~

~~ACCUPRIL 5 mg Reg. No.: 90/7.1.3/00759~~

~~ACCUPRIL 10 mg Reg. No.: 90/7.1.3/00756~~

~~ACCUPRIL 20 mg Reg. No.: 90/7.1.3/00757~~

~~ACCUPRIL 40 mg Reg. No.: 90/7.1.3/00758~~