APPROVED PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAMES AND DOSAGE FORMS:

ACCUMAX® 5 mg Tablet

ACCUMAX® 10 mg Tablet

ACCUMAX® 20 mg Tablet

ACCUMAX® 40 mg Tablet

COMPOSITION:

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

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

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

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

The inactive ingredients are crospovidone, gelatin, lactose monohydrate, magnesium carbonate, magnesium stearate and purified water. The tablets are coated with opadry Y-5-9020 G-Brown and candelilla wax.

Contains sugar (Accumax 10 mg has 76 mg lactose monohydrate per tablets and Accumax 20 mg has 33,336 mg lactose monohydrate per tablet).

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

catalyses 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:

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

INDICATIONS:

Hypertension:

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

Congestive heart failure:

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

CONTRAINDICATIONS:

ACCUMAX is contraindicated in patients who are hypersensitive to this product, including patients with a history of angioedema with ACE-inhibitors.

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 category 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.

Angioedema: Angioedema, including laryngeal oedema, may occur, especially following the first dose of ACCUMAX. 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 ACCUMAX 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 1:1 000 (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.

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: 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.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of ACCUMAX 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 ACCUMAX or any concomitant diuretic therapy should be considered if this event occurs.

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.

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 ACCUMAX. 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.

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 quinapril produces further deterioration in renal function.

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.

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 ACCUMAX alone may have increased serum potassium levels. This effect may help to reduce the hypokalaemia induced by thiazide diuretics. ACCUMAX 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.

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

INTERACTIONS:

Tetracycline: Concomitant administration of tetracycline with ACCUMAX 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 ACCUMAX and tetracycline be avoided.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy due to the sodium-losing effect of these agents. These drugs should be administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: No important pharmacokinetic interactions occurred when ACCUMAX was used concomitantly with propranolol, hydrochlorothiazide, digoxin, or cimetidine. No change in prothrombin time occurred when ACCUMAX 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 ACCUMAX. Hypotensive effects after the first dose of ACCUMAX 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 ACCUMAX.

PREGNANCY AND LACTATION:

Pregnancy: There are no adequate and well-controlled studies in pregnant women. ACCUMAX is contraindicated throughout pregnancy (see WARNINGS AND SPECIAL PRECAUTIONS).

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

Paediatric use: The safety and effectiveness of ACCUMAX in children has not been established.

DOSAGE AND DIRECTIONS FOR USE:

ACCUMAX may be administered without regard to meals.

Hypertension:

Monotherapy: The recommended initial dosage of ACCUMAX 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 ACCUMAX 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 two doses with concomitant therapy.

SIDE EFFECTS:

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

Very common (>1/10), Common (>1/100 and <1/10), Uncommon (>1/1 000 and <1/100), Rare (>1/10 000 and <1/1 000), Very rare (<1/10 000).

Blood and lymphatic system disorders:

Rare: Agranulocytosis, haemolytic anaemia, 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: Chest pain, fatigue.

Uncommon: Oedema (peripheral and generalised)

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 LD_{50} of quinapril in mice and rats ranges from 1 440 to 4 280 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:

ACCUMAX 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.

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

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

ACCUMAX 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, 50, 60, 90 and 100 tablets.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

Type A amendment

ACCUMAX 5 mg: 34/7.1.3/0229

ACCUMAX 10 mg: 34/7.1.3/0230

ACCUMAX 20 mg: 34/7.1.3/0231

ACCUMAX 40 mg: 34/7.1.3/0232

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

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

17 February 2006

BOTSWANA: S2

ACCUMAX 10 mg: Reg. No.: BOT1101980

ACCUMAX 20 mg: Reg. No.: BOT1101979

NAMIBIA: S2

ACCUMAX 5 mg: Reg. No.: 07/7.1.3/0119

ACCUMAX 10 mg: Reg. No.: 07/7.1.3/0118

ACCUMAX 20 mg: Reg. No.: 07/7.1.3/0117

ACCUMAX 40 mg: Reg. No.: 07/7.1.3/0116