FINAL APPROVED PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

ACCUMAX® CO 10/12,5 Tablet

ACCUMAX® CO 20/12,5 Tablet

COMPOSITION:

ACCUMAX CO 10/12,5: Each tablet contains quinapril hydrochloride equivalent to 10 mg quinapril and 12,5 mg hydrochlorothiazide.

ACCUMAX CO 20/12,5: Each tablet contains quinapril hydrochloride equivalent to 20 mg quinapril and 12,5 mg hydrochlorothiazide.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines – other hypotensives

PHARMACOLOGICAL ACTION:

ACCUMAX CO is a fixed-combination tablet that combines an angiotensin-converting enzyme (ACE) inhibitor, quinapril hydrochloride, and a diuretic, hydrochlorothiazide.

Concomitant administration of quinapril and hydrochlorothiazide has no effect on the pharmacokinetics of either drug.

As a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity (PRA), increases aldosterone secretion, and decreases serum potassium.

Administration of quinapril inhibits the renin-angiotensin-aldosterone axis and tends to attenuate the potassium loss associated with hydrochlorothiazide.

Quinapril:

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

Quinapril is rapidly de-esterified 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 de-esterified 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 diminished renal function which occurs in the elderly (see DOSAGE AND DIRECTONS FOR USE). Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification 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.

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic which acts on the kidneys to increase the excretion of sodium and chloride and an accompanying volume of water. Hydrochlorothiazide also increases the loss of potassium, bicarbonate and other electrolytes via the urine, and it decreases calcium excretion. Chronic administration of hydrochlorothiazide elevates plasma renin activity considerably.

Pharmacokinetic properties and metabolism:

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6 to 12 hours. Hydrochlorothiazide is excreted unchanged by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 4 to 15 hours. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Pharmacodynamic properties:

With chronic treatment, hydrochlorothiazide reduces peripheral vascular resistance, mean arterial pressure, and systolic and diastolic blood pressure.

INDICATIONS:

ACCUMAX CO is indicated for the treatment of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions.

CONTRAINDICATIONS:

ACCUMAX CO is contraindicated in patients who are hypersensitive to any component of this product, including patients with a history of angioedema with ACE-inhibitors. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulphonamide-derived agents.

Pregnancy:

Both components of ACCUMAX CO cross the placenta. ACCUMAX CO is contraindicated throughout pregnancy.

Nursing mothers:

Because quinapril and its metabolites as well as hydrochlorothiazide are secreted in human breast milk,

ACCUMAX CO should not be used by breastfeeding women.

Paediatric use:

Safety and effectiveness in children have not been established.

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 medicine.
Should a woman contemplate pregnancy, the doctor should 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.

Quinapril:

Angioedema: Angioedema which may be fatal has been reported in patients treated with ACE-inhibitors, including quinapril. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUMAX CO should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including but not limited to subcutaneous adrenaline injection 1:1 000 (0,3 to 0,5 ml), should be promptly instituted (see SIDE EFFECTS).

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: Symptomatic hypotension is a possible consequence of therapy in salt/volume depleted

patients, such as those previously treated with diuretics or patients on dialysis (see INTERACTIONS and SIDE EFFECTS).

In patients at risk of excessive hypotension, including those with congestive heart failure, therapy should be started under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND DIRECTIONS FOR USE).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of quinapril or reduced concomitant diuretic therapy should be considered.

Neutropenia/agranulocytosis: ACE-inhibitors have been associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE-inhibitors including quinapril, may be associated with oliguria and/or progressive azotaemia and rarely, acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE-inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE-inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, when quinapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or quinapril may be required.

Renal function should be closely monitored in patients with renal impairment, although clinical studies indicate that overall quinapril produces no further deterioration in renal function. 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 quinapril alone may have increased serum potassium levels. When administered concomitantly, quinapril may reduce the hypokalaemia induced by thiazide diuretics. Quinapril has not been studied as concomitant therapy with potassium-sparing diuretics. Because of the risk of further potentiating increases in serum potassium, combination therapy with potassium-sparing diuretics should be initiated with caution and the patient's serum potassium levels closely monitored (see INTERACTIONS). With ACCUMAX CO, which contains both an ACE-inhibitor and a diuretic, the addition of a potassium-sparing diuretic is not recommended.

Surgery/anaesthesia: In patients undergoing anaesthesia with agents that produce hypotension, quinapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide:

Thiazides should be used with caution in patients with severe renal disease since uraemia may result. Cumulative drug effects may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Exacerbation or activation of systemic lupus erythematosus has been reported.

Serum electrolyte evaluation should be performed at appropriate intervals to detect possible electrolyte imbalance.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, including hyponatraemia, hypochloraemic alkalosis, and hypokalaemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalaemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after

prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Hypokalaemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis, for example, increased ventricular irritability. Because quinapril reduces the production of aldosterone, concomitant therapy with quinapril attenuates the diuretic-induced potassium loss (see INTERACTIONS, Agents increasing serum potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatraemia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricaemia may occur or gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Hyperglycaemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident, it may be necessary to withhold or discontinue diuretic therapy.

Thiazides have been shown to increase urinary magnesium excretion, which may cause hypomagnesaemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight serum calcium elevation in the absence of known calcium metabolism disorders. Marked hypercalcaemia may be evident of hidden hyperparathyroidism. Thiazides should be discontinued before performing tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazides decrease the serum PBI levels without signs of thyroid disturbance.

Geriatric use:

Elderly patients exhibited increased AUC and peak levels for quinaprilat compared to values observed 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.

INTERACTIONS:

Quinapril:

Tetracycline: Simultaneous administration of tetracycline with quinapril reduced the absorption of tetracycline by approximately 28 % to 37 % in subjects. Decreased absorption is due to the presence of magnesium carbonate as an excipient in the quinapril formulation. This interaction should be considered when contemplating concurrent ACCUMAX CO and tetracycline therapy.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitory therapy. These drugs should be administered with caution and frequent monitoring of serum lithium levels is recommended. With ACCUMAX CO, which includes a diuretic, the risk of lithium toxicity may be increased.

Other agents: No clinically important pharmacokinetic interactions occurred when quinapril was administered concomitantly with propranolol, hydrochlorothiazide, digoxin, or cimetidine. No change in prothrombin complex activity occurred when quinapril 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 quinapril. Hypotensive effects after the first dose of quinapril 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 CO (see WARNINGS AND SPECIAL PRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE).

Agents increasing serum potassium: Since ACCUMAX CO contains an ACE-inhibitor, the addition of a potassium-sparing diuretic is not recommended.

Hydrochlorothiazide:

When administered concurrently, the following agents may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic agents (oral hypoglycaemic agents and insulin): Dosage adjustments of the antidiabetic drug may be required.

Other antihypertensive agents: Additive effect or potentiation.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. noradrenaline): Possible decreased response to pressor amines, but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Nonsteroidal anti-inflammatory agents: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when ACCUMAX CO and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be closely observed to determine if the desired effect of ACCUMAX CO is obtained.

DOSAGE AND DIRECTIONS FOR USE:

Effective blood pressure control is usually achieved with a daily dosage of 10/12,5 mg to a maximum of 20/25 mg.

Dosage adjustment in renal impairment: ACCUMAX CO should not be used as initial therapy in patients with renal impairment (creatinine clearance < 40 ml/min).

SIDE EFFECTS:

Adverse experiences that have occurred have been limited to those that have been previously reported with quinapril or hydrochlorothiazide.

The most frequent clinical adverse experiences were headache, dizziness, cough, and fatigue. See WARNINGS AND SPECIAL PRECAUTIONS regarding angioedema and excessive hypotension or syncope.

Adverse experiences by bodily systems are listed in descending order of frequency and include the following:

Cardiovascular: Vasodilation, chest pain, tachycardia, postural hypotension, palpitations.

Gastrointestinal: Nausea and/or vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, dry mouth or throat, constipation, pancreatitis, gastro-intestinal disturbances, taste disturbances.

Respiratory: Persistent cough, rhinitis, upper respiratory infection, bronchitis, pharyngitis, dyspnoea, sinusitis.

Integumentary: Erythema multiforme, toxic epidermal necrolysis, exfoliative dermatitis, alopecia, pemphigus, pruritus, skin rashes, hypersensitivity reactions, skin disturbances, cholestatic jaundice, stomatitis.

HCTZ: Stevens-Johnson syndrome.

Nervous/psychiatric: Headache, dizziness, insomnia, somnolence, vertigo, paraesthesia, nervousness, syncope, mood and sleep disturbances.

Urogenital: Impotence, urinary tract infection, urinary abnormality, dysuria, urinary frequency, hyperkalaemia, hyponatraemia, renal failure.

Musculoskeletal: Myalgia, back pain, muscle cramps.

Other: Fatigue, viral infection, asthenia, malaise, arthralgia, peripheral oedema, fever, haemolytic anaemia, blood disorders, neutropenia, agranulocytosis, thrombocytopenia.

In addition, angioedema has been reported in patients receiving quinapril (see WARNINGS AND SPECIAL PRECAUTIONS).

Clinical laboratory test findings:

Serum electrolytes: (see WARNINGS AND SPECIAL PRECAUTIONS).

Creatinine, blood urea nitrogen: Increases (> 1,25 times the upper limit of normal) in serum creatinine and blood urea nitrogen, proteinuria and nephrotic syndrome.

Serum uric acid, glucose, magnesium, cholesterol, triglyceride, protein-bound iodine (PBI), parathyroid function tests and calcium: (see WARNINGS AND SPECIAL PRECAUTIONS).

Other adverse reactions that have been reported with the individual components are listed below:

Quinapril:

In descending order of frequency these were headache, dizziness, coughing, fatigue, rhinitis, nausea and/or vomiting, myalgia, diarrhoea, dyspepsia, insomnia, dyspnoea, back pain, hypotension, depression, increased perspiration and angina pectoris.

Hydrochlorothiazide:

Body as a whole: Weakness, pulmonary oedema, pneumonitis.

Digestive: Anorexia, gastric irritation, thirst, diarrhoea, cramping, jaundice (intra-hepatic cholestatic jaundice), pancreatitis, sialoadenitis, constipation.

Haematologic: Leukopenia, granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic and aplastic anaemia.

Musculoskeletal: Muscle spasm, muscle pain.

Nervous system/psychiatric: Restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS AND SPECIAL PRECAUTIONS).

Special senses: Xanthopsia, yellow vision, photosensitivity reactions.

Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions.

Other: Oliguria, hyperglycaemia, glycosuria, hyperuricaemia, hypochloraemic alkalosis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Quinapril/hydrochlorothiazide:

No data are available with respect to overdosage in humans. The oral median lethal dose of quinapril/hydrochlorothiazide in combination ranges from 1 063/664 to 4 640/2 896 mg/kg in mice and rats.

No specific information is available on the treatment of overdosage with ACCUMAX CO. Treatment is symptomatic and supportive consistent with established medical care. Therapy with ACCUMAX CO should be discontinued and the patient closely observed.

Quinapril:

No data are available with respect to overdosage in humans. The oral median lethal dose 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 would usually be treated by infusion of intravenous normal saline solution.

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

Hydrochlorothiazide:

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

IDENTIFICATION:

ACCUMAX CO 10/12,5: Pink, elliptical, biconvex, film-coated tablets, scored on both sides.

ACCUMAX CO 20/12,5: Pink, triangular, biconvex, film-coated tablets, scored on one side.

PRESENTATION:

ACCUMAX CO 10/12,5: Polyamide/aluminium/PVC blister packs of 28, 30, 50, 60, 90 and 100 tablets.

ACCUMAX CO 20/12,5: Polyamide/aluminium/PVC blister packs of 28, 30, 50, 60, 90, and 100 tablets.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

ACCUMAX CO 10/12,5: 34/7.1.3/0233

ACCUMAX CO 20/12,5: 34/7.1.3/0234

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

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

03 June 2005

BOTSWANA: S2

ACCUMAX CO 10/12,5: Reg. No.: BOT1101950

ACCUMAX CO 20/12.5: Reg. No.: BOT1101951

NAMIBIA: S2

ACCUMAX CO 10/12,5: Reg. No.: 07/7.1.3/0128

ACCUMAX CO 20/12,5: Reg. No.: 07/7.1.3/0129

ZIMBABWE: PP10

ACCUMAX CO 10/12,5: Reg. No.: 2012/12/4715

ACCUMAX CO 20/12,5: Reg. No.: 2012/12/4713