ACCURETIC®

Quinapril/hydrochlorothiazide

SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

ACCURETIC® 10/12.5 (tablet)

ACCURETIC® 20/12.5 (tablet)

COMPOSITION:

ACCURETIC 10/12.5:

Each tablet contains quinapril hydrochloride equivalent to 10 mg quinapril, and 12,5 mg hydrochlorothiazide.

ACCURETIC 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:

ACCURETIC 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 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 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 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.

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:

ACCURETIC 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:

ACCURETIC is contraindicated:

- in patients who are hypersensitive to any components 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 ACCURETIC should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines
- Lithium therapy: Concomitant administration with ACCURETIC 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 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 (see PREGNANCY AND LACTATION).

Quinapril

Head and Neck 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 ACCURETIC 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).

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 during desensitization: Patients receiving ACE inhibitors such as ACCURETIC 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.

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 such as ACCURETIC 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 preexisting 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 preexisting 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.

Hypoglycaemia and Diabetes: ACE inhibitors such as ACCURETIC 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 ACCURETIC, 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).

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 become 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 evidence 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.

Use in the Elderly:

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.

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 ACCURETIC therapy.

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 ACCURETIC and tetracycline therapy.

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 ACCURETIC (see WARNINGS AND SPECIAL PRECAUTIONS).

Agents increasing Serum Potassium: Since ACCURETIC contains an ACE-inhibitor, the addition of a potassium-sparing diuretic is not recommended (see CONTRAINDICATIONS).

Hydrochlorothiazide

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

Alcohol, Barbiturates, or Narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral hypoglycaemic agents and insulin) - dosage adjustments of the antidiabetic drug may be required.

Other Antihypertensive Drugs - 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, Nondepolarizing (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 Drugs - 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 ACCURETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of ACCURETIC is obtained.

PREGNANCY AND LACTATION:

Pregnancy: Both components of ACCURETIC cross the placenta. ACCURETIC is contraindicated throughout pregnancy (see WARNINGS AND SPECIAL PRECAUTIONS).

Nursing Mothers: Because quinapril and its metabolites as well as hydrochlorothiazide are secreted in human breast milk, ACCURETIC should not be used by breastfeeding women.

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

Use in Children:

Safety and effectiveness have not been established in children.

SIDE EFFECTS:

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

In controlled clinical trials, the most frequent clinical adverse experiences were headache, dizziness,

cough, and fatigue.

Adverse events reported have been categorised as follows:

Very common: ≥ 1/10 (≥ 10 %); Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %); Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %); Very Rare: < 1/10 000 (< 0,01 %)

MeDRA System Organ Class	**Frequency**	**Adverse Event**
Nervous system disorders	Common	Headache, dizziness, insomnia, somnolence, vertigo
	Uncommon	Paraesthesia, nervousness, syncope
Cardiac disorders	Common	Vasolidation, chest pain
	Uncommon	Tachycardia, palpitations, hypotension, postural hypotension
Respiratory, thoracic and mediastinal disorders	Common	Cough, rhinitis, upper respiratory infection, bronchitis, pharyngitis
	Uncommon	Dyspnoea, sinusitis
Gastrointestinal disorders	Common	Nausea and/or vomiting, abdominal pain, diarrhoea, dyspepsia
	Uncommon	Flatulence, dry mouth or throat, constipation, pancreatitis
Skin and subcutaneous disorders	Uncommon	Erythema multiforme, exfoliative dermatitis, alopecia, pemphigus, pruritus HCTZ: Stevens-Johnson syndrome
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia, back pain
Renal and urinary disorders	Uncommon	Urinary tract infection, urinary abnormality, dysuria, urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence

General disorders and administrative site conditions	Common	Fatigue, viral infection, asthenia
	Uncommon	Malaise, arthralgia, peripheral oedema, fever
Investigations	Uncommon	Serum electrolytes, creatinine, blood urea nitrogen (increases > 1,25 times the upper limit of normal), serum uric acid, glucose, magnesium, cholesterol, triglyceride, protein-bound iodine (PBI), parathyroid function tests and calcium

See (WARNINGS AND SPECIAL PRECAUTIONS) regarding angioedema and excessive hypotension or syncope.

The following additional adverse events have been reported during Post-Marketing Surveillance:

Blood and lymphatic system disorders: Haemolytic anaemia, thrombocytopenia

Immune system disorders: anaphylactic reaction

Hepatobiliary disorders: hepatitis

Skin and subcutaneous tissue disorders: photosensitivity reaction

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

Quinapril:

Psychiatric disorders: depression

Nervous system disorders: headache, dizziness, insomnia

Cardiac disorders: hypotension, angina pectoris

Respiratory, thoracic and mediastinal disorders: cough, rhinitis, dyspnoea

Gastrointestinal disorders: nausea and/or vomiting, diarrhoea, dyspepsia

Musculoskeletal, connective tissue and bone disorders: myalgia, back pain

General disorders and administrative site conditions: fatigue, increased perspiration

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

Hydrochlorothiazide:

Blood and the lymphatic system disorders: leukopenia, agranulocytosis, thrombocytopenia, aplastic

anaemia, haemolytic anaemia

Immune system disorders: anaphylactic reactions

Nervous system disorders: restlessness

Eye disorders: xanthopsia

Respiratory, thoracic and mediastinal disorders: respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders: anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, constipation

Skin and subcutaneous tissue disorders: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis)

Musculoskeletal, connective tissue and bone disorders: muscle spasm

Renal and urinary disorders: renal failure, renal dysfunction, interstitial nephritis (see WARNINGS AND SPECIAL PRECAUTIONS)

General disorders and administrative site conditions: weakness

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 ACCURETIC. Treatment is symptomatic and supportive consistent with established medical care. Therapy with ACCURETIC should be discontinued and the patient observed closely.

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:

ACCURETIC 10/12.5: Pink, elliptical, biconvex, film-coated tablets, scored on both sides.

ACCURETIC 20/12.5: Pink, triangular, biconvex, film-coated tablets, scored on one side.

PRESENTATION:

ACCURETIC 10/12.5: Blister packs of 28 tablets.

ACCURETIC 20/12.5: Blister packs of 28 tablets.

STORAGE INSTRUCTIONS:

Store in a cool (below 30 °C), dry place.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ACCURETIC 10/12.5: 27/7.1.3/0165

ACCURETIC 20/12.5: 27/7.1.3/0166

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:

23 July 2010

BOTSWANA: S2

ACCURETIC 10/12.5 tablets – Reg. No. BOT9700035

ACCURETIC 20/12.5 tablets – Reg. No. BOT9700036

NAMIBIA: S2

ACCURETIC 10/12.5 tablets – Reg. No. 04/7.1/1219

ACCURETIC 20/12.5 tablets – Reg. No. 04/7.1/1220