

PRODUCT INFORMATION

ACCURETIC[®]

(quinapril hydrochloride + hydrochlorothiazide)

DESCRIPTION

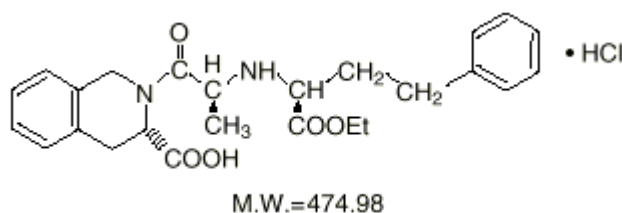
ACCURETIC is a fixed-combination tablet that combines an angiotensin-converting enzyme inhibitor, quinapril hydrochloride, and a diuretic, hydrochlorothiazide (HCTZ).

ACCURETIC is available in two tablet strengths:

ACCURETIC 10/12.5 containing quinapril 10 mg / hydrochlorothiazide 12.5 mg.

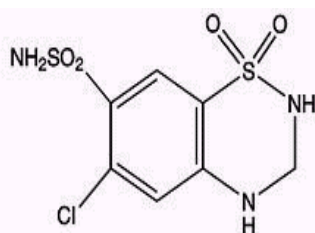
ACCURETIC 20/12.5 containing quinapril 20 mg / hydrochlorothiazide 12.5 mg.

Quinapril hydrochloride (CAS no. 82586-55-8) is chemically described as 2-(S)-[N-[[1-ethoxycarbonyl]-3-phenylpropyl]-(S)-alanyl]-1,2,3,4-tetrahydro-3-(S)-isoquinoline carboxylic acid, monohydrochloride. Its empirical formula is $C_{25}H_{30}N_2O_5 \cdot HCl$ and its structural formula is:



Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents.

Hydrochlorothiazide (CAS no. 58-93-5) is chemically described as 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



M.W.=297.72

Hydrochlorothiazide is a white to off-white, crystalline powder that is slightly soluble in water, but freely soluble in sodium hydroxide solution.

ACCURETIC tablets also contain crospovidone, lactose, magnesium carbonate, magnesium stearate, povidone, candelilla wax and Opadry Pink OY-S-6937.

PHARMACOLOGY

Pharmacodynamics

In clinical studies, concomitant administration of quinapril and hydrochlorothiazide produced greater reductions in blood pressure than the single agents given alone.

As a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity (PRA), increases aldosterone secretion, decreases serum potassium and increases urinary potassium loss. Administration of quinapril inhibits the renin-angiotensin-aldosterone axis and tends to attenuate the potassium decrease associated with hydrochlorothiazide.

Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of angiotensin-converting enzyme (ACE) activity in human and animal studies. ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, noradrenaline or adrenaline. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with quinapril alone resulted in mean increases in potassium of 0.07 mmol/L (see **PRECAUTIONS**). Removal of angiotensin II negative feedback on renin secretion leads to increased PRA.

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. Quinapril monotherapy was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in nonblacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator. Bradykinin acts on bradykinin receptors in the vascular endothelium to promote the release of the vasodilators such as nitric oxide and prostacyclin. Whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

ACE inhibitors, including quinapril may enhance insulin sensitivity.

In a study in spontaneously hypertensive rats, the magnitude of the antihypertensive effect of quinapril correlated more closely with inhibition of tissue ACE than inhibition of plasma ACE.

Pharmacokinetics

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

Absorption

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%. The absorption of hydrochlorothiazide is somewhat slower (1 to 2.5 hours) and more complete (50-80%).

The rate of quinapril absorption was reduced by 14% when ACCURETIC tablets were administered with a high fat meal as compared to fasting, while the extent of absorption was not affected. The rate of hydrochlorothiazide absorption was reduced by 12% when ACCURETIC tablets were administered with a high fat meal, while the extent of absorption was not significantly affected. Therefore, ACCURETIC may be administered without regard to food.

Distribution

Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins. Hydrochlorothiazide is 68% bound to plasma proteins and has an apparent volume of distribution of 0.83 to 1.141 L/kg.

Metabolism

Following absorption, 38% of orally administered quinapril is systemically available as quinaprilat. Peak plasma quinaprilat concentrations are observed approximately two hours following an oral dose of quinapril. Hydrochlorothiazide is not metabolised.

Elimination

Quinaprilat has an apparent elimination half-life in plasma of approximately 2 hours, representing the clearance of the free quinaprilat from the plasma and a prolonged terminal phase with a half-life of 25 hours thought to reflect the slow release of quinaprilat from ACE. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of three hours following multiple oral dosing of quinapril.

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.

Special Populations

Renal Impairment

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. Pharmacokinetic studies in patients with end-stage renal disease on chronic haemodialysis or continuous ambulatory peritoneal dialysis indicate that dialysis has little effect on the elimination of quinapril and quinaprilat (see **PRECAUTIONS, Impaired Renal Function** and **DOSAGE AND ADMINISTRATION, Use in Renal Impairment**).

Hepatic Impairment

Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril (see **PRECAUTIONS, Impaired Hepatic Function**).

Elderly (≥ 65 years)

Elimination of quinaprilat is reduced in elderly patients (≥ 65 years) and correlates well with their level of renal function (see **PRECAUTIONS, Use in the Elderly** and **DOSAGE AND ADMINISTRATION**).

Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Clinical Effects

Administration of 10 to 80 mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. 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. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24-hour dosing interval and continue during long-term therapy. Therapeutic effects of quinapril appear to be the same for elderly (≥ 65 years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

Haemodynamic assessments in patients with hypertension have indicated that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction.

The mechanism underlying the antihypertensive activity of diuretics is unknown. During chronic administration peripheral vascular resistance is reduced; however, this may be secondary to changes in sodium balance.

Hydrochlorothiazide is a diuretic that acts directly on the kidney to increase excretion of sodium and chloride and an accompanying volume of water. Hydrochlorothiazide also increases the excretion of potassium and bicarbonate and decreases calcium excretion. Chronic treatment with hydrochlorothiazide elevates PRA two- to six-fold. After oral administration of hydrochlorothiazide, diuresis begins within two hours, peaks in about four hours and lasts about six to twelve hours.

Combination therapy with quinapril and hydrochlorothiazide gives a blood pressure lowering effect greater than that seen with either agent alone.

INDICATIONS

ACCURETIC is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

CONTRAINDICATIONS

ACCURETIC is contraindicated in:

- Patients who are hypersensitive to either quinapril hydrochloride and/or hydrochlorothiazide
- Patients with a history of hereditary and/or idiopathic angioedema or angioedema related to previous treatment with ACE inhibitors
- Severe renal artery stenosis
- Due to the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs
- Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes (see **PRECAUTIONS, Anaphylactoid Reactions - Haemodialysis**).
- Pregnancy (see **PRECAUTIONS, Use in Pregnancy**). Women who intend to become pregnant, or of childbearing potential, unless on an effective contraceptive and highly unlikely to conceive.

PRECAUTIONS

Angioedema

Since 1984, severe life-threatening angioedema has been reported with most of the ACE inhibitors. The overall incidence with some of the ACE inhibitors is approximately 0.1 to 0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema is nonpitting oedema of the skin, mucous membrane or subcutaneous tissue.

The onset of angioedema associated with the use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. Angioedema may occur with or without urticaria.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors. In such cases the product should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema can be fatal or near fatal. There seems to be no difference in the incidence of angioedema in patients of either sex or in those with heart failure or hypertension. In the majority of reported cases the symptoms occurred during the first week of therapy.

In USA studies, black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. It should also be noted that,

in controlled clinical trials conducted in Europe and North America, ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

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 has been no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. 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.

There are reports where switching to another ACE inhibitor was followed by recurrence of oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see **CONTRAINDICATIONS**). Where involvement of tongue, glottis or larynx is likely to cause airway obstruction, appropriate therapy, including adrenaline and oxygen administration, should be carried out promptly or the patient hospitalised. Medical therapy of progressive angioedema should be aggressive. Failing a rapid response, oral/nasal intubation or securing an airway by surgical means (e.g. cricothyrotomy or tracheostomy) may be necessary followed by mechanical ventilation. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

Hypotension

ACCURETIC can cause symptomatic hypotension, usually not more frequently than either drug as monotherapy. Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with quinapril but is a possible consequence of ACE inhibition therapy in salt/volume depleted patients such as those previously treated with diuretics, who have a dietary salt restriction, or who are on dialysis (see **PRECAUTIONS, Interactions with Other Medicines, and ADVERSE EFFECTS**).

ACCURETIC should be used cautiously in patients receiving concomitant therapy with other antihypertensive agents. The thiazide component of ACCURETIC may potentiate the action of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. The antihypertensive effects of the thiazide component may also be enhanced in the post-sympathectomy patients.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy for hypertension may cause an excessive drop in blood pressure, which may be associated with oliguria, azotemia, and in rare instances, with acute renal failure and death in such patients. ACCURETIC therapy should be started under close medical supervision. Patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased.

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 the drug should be considered if this event occurs.

Anaphylactoid Reactions

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

- Desensitisation - Patients receiving ACE inhibitors during desensitising 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.
- LDL aphaeresis - Patients undergoing low-density lipoprotein apheresis with dextran-sulfate absorption when treated concomitantly with an ACE inhibitor, have reported anaphylactoid reactions.
- 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 therefore not be used (see **CONTRAINDICATIONS**). The use of alternative antihypertensive drugs, or alternative membranes for haemodialysis is recommended (e.g. cuprophane or polysulphone PSF).

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Impaired Renal Function

ACCURETIC is not recommended in patients with severe renal disease. Thiazides may precipitate azotemia in such patients, and the effects of repeated dosing may be cumulative.

Some quinapril-treated hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially 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. Evaluation of the hypertensive patient should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

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, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death (see **ADVERSE EFFECTS**).

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <60 mL/min require a lower initial dosage of the drug (see **DOSAGE AND ADMINISTRATION**). These patients dosage should be titrated upwards based upon therapeutic response; renal function should be closely monitored although initial studies do not indicate that the drug produces further deterioration in renal function.

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 (see **ADVERSE EFFECTS**).

Impaired Hepatic Function

ACCURETIC 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. Also, since the metabolism of quinapril to quinaprilat is normally dependent upon hepatic esterase, patients with impaired liver function could develop markedly elevated plasma levels of quinapril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Foetal/Neonatal Morbidity and Mortality

See **PRECAUTIONS, Use in Pregnancy**.

Cough

Cough has been reported with the use of ACE inhibitors, including quinapril. Characteristically, the cough is persistent dry, non-productive, and resolves after discontinuation of therapy. The frequency of reports has been increasing since cough was first recognised as a side effect of ACE inhibitor therapy. In various studies, the incidence of cough varies between 2 to 15% depending on the drug, dosage and duration of use. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for two-thirds of the reported cases). Patients who cough may have increased bronchial reactivity compared to those who do not. The observed higher frequency of this side effect in non-smokers may be due to a higher level of tolerance in smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins that accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drug may be required in severe cases.

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.

Serum Electrolytes

Serum electrolyte evaluation should be performed at appropriate intervals to detect possible electrolyte imbalance. As with other ACE inhibitors, patients on quinapril alone may have increased serum potassium levels. In clinical trials, hyperkalaemia (serum potassium ≥ 5.8 mmol/L) occurred in approximately 2% of patients receiving quinapril. In most cases, elevated serum potassium levels were isolated values that resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalaemia. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes. The addition of a potassium-sparing diuretic to ACCURETIC, which contains a diuretic, is not recommended.

Conversely, treatment with thiazide diuretics has been associated with hypokalaemia, hyponatremia, and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of the following: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, confusion, seizures and vomiting. Hypokalaemia can also sensitise or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or adrenocorticotrophic hormone (ACTH).

The opposite effects of quinapril and hydrochlorothiazide on serum potassium will approximately balance each other in many patients so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant. Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Chloride deficits secondary to thiazide therapy are generally mild and require specific treatment only under extraordinary circumstances (e.g. in liver disease or renal disease). Dilutional hyponatremia may occur in oedematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Calcium excretion is decreased by thiazides. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen.

Thiazides should be discontinued before performing tests for parathyroid function.

Thiazides increase the urinary excretion of magnesium, and hypomagnesaemia may result (see **PRECAUTIONS**).

Other Metabolic Disturbances

Thiazide diuretics tend to reduce glucose tolerance and to raise serum levels of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout or overt diabetes may be precipitated in susceptible patients.

Neutropenia/Agranulocytosis

ACE inhibitors have been rarely associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Agranulocytosis has been rarely reported during treatment with quinapril. As with other ACE inhibitors, periodic monitoring of white blood cell counts in quinapril-treated patients with collagen vascular disease and/or renal disease should be considered.

Dermatological Reactions

Dermatological reactions characterised by maculopapular pruritic rashes and sometimes photosensitivity have been reported rarely with ACE inhibitors. Rare and sometimes severe skin reactions (e.g. lichenoid eruptions, psoriasis, pemphigus-like rash, and rosacea, Stevens-Johnson syndrome) have also been reported. A causal relationship is difficult to assess.

A cutaneous reaction to one ACE inhibitor may not occur with another drug of the same class. There have, however, been reports of cross-reactivity.

Taste Disturbance (Dysgeusia)

The incidence of taste disturbance was reported to be high (up to 12.5%) with high doses of one ACE inhibitor, but the overall incidence for the class is probably low (< 0.5%). However, the relevant data are scarce and difficult to interpret.

Taste disturbance has been described as a suppression of taste or a metallic sensation in the mouth. The dysgeusia usually occurs in the first few weeks of treatment and may disappear within 1 to 3 months despite continued treatment.

Surgery/Anaesthesia

Caution should be exercised when patients undergo major surgery or anaesthesia since angiotensin converting enzyme inhibitors have been shown to block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension that can be corrected by volume expansion.

Acute Myopia and Secondary Angle-Closure Glaucoma*

Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-close glaucoma can lead to permanent vision loss. The

primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Valvular Stenosis

Patients with aortic stenosis are at a particular risk of decreased coronary perfusion and hypotension when treated with vasodilators. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain. Nevertheless, ACE inhibitors should be avoided in such patients.

Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Dual Blockade of the Renin-angiotensin-aldosterone System*

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals with congestive heart failure, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled symptoms of heart failure and should be limited to individually defined cases with close monitoring of renal function.

Carcinogenesis, Mutagenicity, Impairment of Fertility

Carcinogenicity and mutagenicity studies of quinapril in combination with hydrochlorothiazide have not been conducted in animals.

At least one other ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in humans is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign.

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day for 104 weeks. Female rats given the highest dose level have an increased incidence of mesenteric lymph node haemangiomas and skin/subcutaneous lipomas. Neither

quinapril nor quinaprilat are mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation; sister chromatid exchange in cultured mammalian cells; micronucleus test with mice; *in vitro* chromosome aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow.

With hydrochlorothiazide, two year feeding studies in mice and rats uncovered no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600 mg/kg/day.

Hydrochlorothiazide was not genotoxic in a gene mutation assay in bacterial cells, or in tests for clastogenic activity *in vitro* and *in vivo*. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and non-disjunction assay in *Aspergillus nidulans*).

The effects of hydrochlorothiazide and the quinapril/hydrochlorothiazide combination on fertility have not been evaluated in animal studies. However, with quinapril alone, there were no adverse effects on fertility or reproduction in rats at oral doses up to 100 mg/kg/day.

Use in Pregnancy

Category D

As with all ACE inhibitors, ACCURETIC is contraindicated in pregnancy (see **CONTRAINDICATIONS**). Pregnancy should be excluded before starting treatment with ACCURETIC and avoided during the treatment. If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. When pregnancy is detected, the ACE inhibitor should be discontinued as soon as possible and arrangements for further care should be made.

Infants exposed to ACE inhibitors during pregnancy may be at an increased risk for malformations of the cardiovascular system and central nervous system. A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during first trimester compared with no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared with no exposure.

There have also been reports of prematurity, hypotension, renal system disorders (including renal failure), skull hypoplasia, oligohydramnios, limb contractures, craniofacial deformities, hypoplastic lung development, intrauterine growth retardation, patent ductus arteriosus, foetal death and/or death in the newborn in association with the maternal use of ACE inhibitors.

Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalaemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic effects to the foetus may include foetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

Use in Lactation

ACE inhibitors, including quinapril, are secreted in human milk to a limited extent. Thiazides appear in human milk. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue ACCURETIC or discontinue nursing, taking into account the importance of the drug to the mother.

Use in the Elderly

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to be related to decreased renal function rather than to age itself. Of the total number of patients who received ACCURETIC in clinical trials, 15% were 65 or older, while 1.5% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Paediatric Use

The safety and effectiveness of ACCURETIC in children have not been established.

Interactions with Other Medicines

Tetracycline and Other Drugs that Interact with Magnesium

Administration of tetracycline with quinapril reduced the absorption of tetracycline by approximately 28% to 37%. 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 therapy with ACCURETIC and tetracycline or other drugs that interact with magnesium.

Lithium

Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. 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. With ACCURETIC, the risk of lithium toxicity may be increased. ACCURETIC should be administered with caution and frequent monitoring of serum lithium levels is recommended.

Agents Affecting Sympathetic Activity

Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neurone blocking agents) may be used with caution. Beta-adrenergic blocking drugs will increase the antihypertensive effect of ACE inhibitors, and therefore the patient will need to be closely supervised.

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.

Agents Increasing Serum Potassium

If concomitant therapy of quinapril with potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see **PRECAUTIONS**). Since ACCURETIC contains a diuretic, the addition of a potassium-sparing diuretic is not recommended.

Anion Exchange Resins

Absorption of hydrochlorothiazide is impaired in the presence of anion exchange resins, such as cholestyramine and colestipol. Single doses of the resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Other Agents

No clinically important pharmacokinetic interactions occurred when quinapril was used concomitantly with propranolol, hydrochlorothiazide, digoxin or cimetidine. The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril co-administration twice daily.

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, non-depolarising (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant.

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.

ADVERSE EFFECTS

ACCURETIC has been evaluated for safety in 1571 patients in controlled and uncontrolled studies. In clinical trials with ACCURETIC, no adverse experience specific to the combination has been observed. Adverse experiences that have occurred have been limited to those previously reported with quinapril or hydrochlorothiazide. In controlled trials, the most frequent adverse experiences reported in at least 1% of patients with any combination of quinapril and hydrochlorothiazide were headache (6.7%), dizziness (4.8%), cough (3.2%), and fatigue (2.9%). It should be noted that characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Generally, adverse experiences were mild and transient in nature, and there was no relationship between side effects and age, sex, race, or duration of therapy (see **PRECAUTIONS** regarding angioedema and excessive hypotension or syncope).

Discontinuation of therapy due to adverse effects was required in approximately 2% of patients. Headache (0.5%) was the most common reason for withdrawal followed by cough and nausea and/or vomiting (0.2%). Adverse experiences occurring in $\geq 1\%$ of patients treated with ACCURETIC in controlled trials are shown below (n=943).

Percent of Patients in Controlled Trials

	ACCURETIC (n=943)	PLACEBO (n=100)
Headache	6.7	30.0
Dizziness	4.8	4.0
Coughing	3.2	2.0
Fatigue	2.9	3.0
Myalgia	2.4	5.0
Viral Infection	1.9	4.0
Rhinitis	2.0	3.0
Nausea and/or Vomiting	1.8	6.0
Abdominal Pain	1.7	4.0
Back Pain	1.5	2.0
Diarrhoea	1.4	1.0
Upper Respiratory Infection	1.3	4.0
Insomnia	1.2	2.0
Somnolence	1.2	0.0
Bronchitis	1.2	1.0
Dyspepsia	1.2	2.0
Asthenia	1.1	1.0
Pharyngitis	1.1	2.0
Vasodilatation	1.0	1.0
Vertigo	1.0	2.0
Chest Pain	1.0	2.0

Clinical adverse experiences probably, possibly, or definitely related or of uncertain relationship to therapy, occurring in 0.5% to ≤1.0% of patients treated with quinapril plus hydrochlorothiazide in controlled and uncontrolled trials and less frequently clinically significant events seen in clinical trials, post marketing experience, or with hydrochlorothiazide included:

Blood and lymphatic system disorders	Haemolytic anaemia, thrombocytopenia
Cardiac disorders	Palpitations, tachycardia
Congenital, familial, and genetic disorders	See CONTRAINDICATIONS and PRECAUTIONS, Use in Pregnancy
Gastrointestinal disorders	Dry mouth or throat, flatulence, pancreatitis
General disorders and administration site conditions	Peripheral oedema
Hepato-biliary disorders	Hepatitis
Immune system disorders	Anaphylactoid reaction
Musculoskeletal and connective tissue disorders	Arthralgia
Nervous system disorders	Paraesthesia
Psychiatric disorders	Nervousness
Renal and urinary disorders	Urinary tract infection (see PRECAUTIONS)
Reproductive system and breast disorders	Impotence
Respiratory, thoracic and mediastinal disorders	Dyspnoea, sinusitis
Skin and subcutaneous tissue disorders	Alopecia, erythema multiforme, exfoliative dermatitis, pemphigus, photosensitivity reaction, pruritus, rash (hydrochlorothiazide), Stevens Johnson syndrome
Vascular disorders	Hypotension, syncope

Post-marketing Experience

Adverse reactions that have been reported post-marketing with ACCURETIC which are not listed above, regardless of causality, include the following:

Body as a Whole: face oedema, tongue oedema, angioedema and oedema.

Haematological: leukopenia.

Renal: Acute kidney failure.

Laboratory Findings

Serum Electrolytes: See **PRECAUTIONS**.

Creatinine, Blood Urea Nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 3% and 4% respectively, of patients treated with ACCURETIC (see **PRECAUTIONS**).

Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglyceride, PBI, Parathyroid Function Tests and Calcium: See **PRECAUTIONS**.

Haematology: See **PRECAUTIONS**.

Quinapril has been evaluated for safety in 4960 subjects and patients and was well tolerated. Of these, 3203 patients including 655 elderly patients, participated in controlled clinical trials. Quinapril has been evaluated for long-term safety in over 1400 patients treated for one year or more.

Other Adverse Events Reported when Quinapril is Taken Separately

The following adverse events, other than those listed above for ACCURETIC, have been reported with quinapril therapy as probably, possibly, or definitely related, or of uncertain relationship to therapy in 0.5 to ≤1.0% of patients in both hypertension and/or heart failure studies.

Blood and lymphatic system disorders	Agranulocytosis
Cardiac disorders	Angina pectoris, cardiac rhythm disturbances, cardiogenic shock, heart failure, hyperkalaemia, myocardial infarction
Eye disorders	Amblyopia
Gastrointestinal disorders	Constipation, gastrointestinal haemorrhage
Hepatobiliary disorders	Hepatic failure
Infections and infestations	Pharyngitis
Investigations	Abnormal liver function tests
Nervous system disorders	Cerebrovascular accident, somnolence, vertigo
Psychiatric disorders	Depression
Renal and urinary disorders	Worsening renal failure (see PRECAUTIONS)
Respiratory, thoracic and mediastinal disorders	Eosinophilic pneumonitis
Skin and subcutaneous tissue disorders	Dermatopolymyositis, increased perspiration
Vascular disorders	Hypertensive crisis, orthostatic hypotension, vasodilatation

Other Adverse Events Reported when Hydrochlorothiazide is Taken Separately

The following adverse events, other than those listed above for ACCURETIC, have been reported with hydrochlorothiazide.

Body as a Whole: Fever.

Cardiovascular: Hypotension including orthostatic hypotension, necrotising angitis.

Gastrointestinal: Anorexia, constipation, gastric irritation, jaundice (intrahepatic cholestatic jaundice) and sialoadenitis.

Haematological: Agranulocytosis, aplastic anaemia and purpura.

Integumentary: Urticaria, toxic epidermal necrolysis.

Metabolic: Glycosuria, hyperglycaemia, hyperuricaemia, hyponatraemia and hypokalaemia.

Nervous/Psychiatric: Xanthopsia.

Renal: Interstitial nephritis, renal dysfunction.

Respiratory: Respiratory distress (including pneumonitis and pulmonary oedema).

Other: Muscle spasm, restlessness and transient blurred vision.

DOSAGE AND ADMINISTRATION

Patients not Currently Receiving a Diuretic

For patients not currently receiving a diuretic, whether or not they have been receiving quinapril monotherapy, the recommended initial dosage of ACCURETIC is one ACCURETIC 10/12.5 tablet once daily, taken with or without food. If blood pressure is not adequately controlled, the dose may be increased to one ACCURETIC 20/12.5 tablet once daily and then to two ACCURETIC 10/12.5 tablets once daily if necessary. Further dose increases are not expected to produce any additional reduction in blood pressure.

The score lines on ACCURETIC 10/12.5 tablets allow the tablets to be halved for the administration of a low starting dose in patients who are already taking a diuretic (see below). The score line on ACCURETIC 20/12.5 tablets is for identification purposes only. ACCURETIC 20/12.5 should not be prescribed as half tablets.

Patients Currently Receiving a Diuretic or Who are Volume- or Salt-depleted

Patients who are volume- or salt-depleted should be adequately hydrated before starting ACCURETIC.

In patients who are currently being treated with a diuretic, the diuretic should be discontinued 2 to 3 days before starting treatment with one ACCURETIC 10/12.5 tablet once daily. Once blood pressure has stabilised, the dose of ACCURETIC may be titrated as usual.

If the diuretic cannot be discontinued, quinapril should be added at an initial dose of 2.5 to 5 mg once daily to minimise the potential for hypotension, and patients changed to ACCURETIC when they reach doses equivalent to those provided by the combination tablets. Alternatively, patients may be started on ACCURETIC at a dose of 5/6.25 (half a 10/12.5 tablet) once daily, then titrated upwards. In either case, the first dose should be given under medical supervision and patients observed until blood pressure has stabilised because of the risk of hypotension.

Use in Renal Impairment

Dosage modification is not required in patients with mild to moderate renal impairment (creatinine clearance 30-60 mL/min). ACCURETIC is not recommended in patients with severe renal impairment (creatinine clearance <30mL/min).

When concomitant diuretic therapy is required in such patients, a loop diuretic rather than a thiazide diuretic is preferred for use with quinapril.

OVERDOSAGE

No specific information is available on overdosage with ACCURETIC.

Available data suggest that ACCURETIC overdosage, due to its ACE inhibitor component might be expected to produce severe hypotension.

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

Treatment is symptomatic and supportive. Dehydration and electrolyte imbalance should be treated by established procedures. Hypotension would normally be treated by intravenous volume expansion, such as an infusion of normal saline, with established procedures being implemented to treat persistent hypotension. Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose. No data are available to suggest physiological manoeuvres (e.g. manoeuvres to change pH of the urine) that might accelerate elimination of quinapril and its metabolites would be effective. Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. In a case report of a patient with end-stage renal failure, toxicity due to inadvertently high-dose hydrochlorothiazide treatment was successfully managed by haemodialysis.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

ACCURETIC 10/12.5 tablets: Pink, oval, biconvex, film-coated tablets, scored on both sides. Each tablet contains 10 mg of quinapril and 12.5 mg of hydrochlorothiazide, blister pack of 7s, 10s and 30s.

ACCURETIC 20/12.5 tablets: Pink, triangular, biconvex, film-coated tablets, scored on one side. Each tablet contains 20 mg of quinapril and 12.5 mg of hydrochlorothiazide, blister pack of 7s, 10s and 30s.

Not all pack sizes are being distributed in Australia.

Tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 5000 8422 348
38-42 Wharf Road
West Ryde NSW 2114

POISON SCHEDULE

Schedule 4.

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration 19 March 2002.

Date of Most Recent Amendment: 20 May 2011.

* Please note change to Product Information.

®Registered Trademark of Warner Lambert Company U.S.A.