

# DATA SHEET

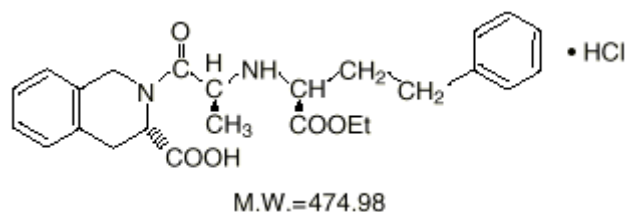
## ACCUPRIL<sup>®</sup>

### Quinapril Hydrochloride Tablets

#### Description

ACCUPRIL (quinapril hydrochloride) is the hydrochloride salt of quinapril, the ethyl ester of a nonsulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat.

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)-isoquinolinecarboxylic acid, monohydrochloride. It is chemically and pharmacologically related to enalapril. Its empirical formula is  $C_{25}H_{30}N_2O_5 \cdot HCl$  and molecular weight is 475.0. Its structural formula is:



Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents. The drug molecule contains three chiral centres but is present as the pure S-S-S-stereoisomer.

ACCUPRIL tablets also contain magnesium carbonate, lactose, gelatin, crospovidone, magnesium stearate, candelilla wax and Opadry Y-5-0920.

#### Clinical Pharmacology

##### Pharmacodynamics

Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. 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 ACCUPRIL 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 plasma renin activity (PRA).

ACCUPRIL has been shown to be effective in the treatment of congestive heart failure and hypertension. 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. ACCUPRIL was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in non-blacks. 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.

**Endothelial Dysfunction:** Endothelial dysfunction is associated with hypertension and heart failure and is considered an important pathophysiological mechanism in cardiovascular disease. Quinapril has been shown to improve endothelium-dependent vasomotor function by mechanisms leading to increased availability of nitric oxide. The clinical significance of improving endothelial function has not yet been established.

In patients with chronic heart failure (NYHA function class III) (n=40), intra-arterial infusion of quinaprilat 1.6 µg/min (n=15) significantly increased endothelium mediated flow-dependent dilation (FDD) in the radial artery by >40% (change in FDD: quinapril = 10.2±0.6% versus control = 6.9±0.6%; p<0.01). In a six month placebo-controlled trial (n=105), normotensive patients, with and without a history of hypertension, who were free of left ventricular dysfunction and severe dyslipidaemia and who required percutaneous coronary artery revascularisation, were treated with quinapril 40 mg daily (n=51). There was an endothelium-dependent reduction of acetylcholine-induced intra-arterial vasoconstriction of the coronary arteries (4.5±3.0% and 12.1±3.0% at 10<sup>-6</sup> and 10<sup>-4</sup> mol/L respectively; overall p=0.002) (TREND study). Flow-mediated vasodilation (FMD) of the brachial artery was significantly increased to 9.1% from a baseline of 7.3% (change in FMD: 1.8 ± 1.0%; p<0.02) in patients with coronary artery disease treated with quinapril 20 mg daily (n=56) for 8 weeks in a partial-block, cross-over, blinded study of 80 patients comparing the effect of four anti-hypertensives on brachial flow-mediated vasodilation (BANFF study).

## Clinical Effects

Single doses of 20 mg of ACCUPRIL provide over 80% inhibition of plasma ACE for 24 hours. Inhibition of the pressor response to angiotensin I is shorter-lived, with a 20 mg dose giving 75% inhibition for about 4 hours, 50% inhibition for about 8 hours, and 20% inhibition at 24 hours. With chronic dosing, however, there is substantial inhibition of angiotensin II levels at 24 hours by doses of 20-80 mg.

**Hypertension:** Administration of 10 to 40 mg ACCUPRIL to patients with essential 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 throughout the 24-hour dosing interval and continue during long-term therapy with no evidence of tolerance.

Haemodynamic assessments in patients with hypertension indicate 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.

Use of ACCUPRIL with a thiazide diuretic gives a blood-pressure lowering effect greater than that seen with either agent alone.

In patients with hypertension, ACCUPRIL 10-40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.

Therapeutic effects appear to be the same for elderly ( $\geq 65$  years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

**Heart Failure:** When compared with placebo therapy, ACCUPRIL administration to patients with congestive heart failure in most controlled studies has prolonged exercise time only modestly, or not at all. On the other hand, the cessation of ACCUPRIL therapy in patients stabilised on this therapy together with diuretic therapy has been shown to result in progressive clinical deterioration in the control of heart failure. While some short-term placebo controlled studies have demonstrated significant improvements in NYHA functional class with ACCUPRIL therapy, other studies have not. In longer term but controlled studies, more consistent improvements in NYHA functional class with ACCUPRIL therapy have been demonstrated. There is a lack of data to support an improved prognosis in congestive heart failure. The effects of quinapril on long-term mortality in heart failure have not been evaluated.

## Pharmacokinetics

The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5-80 mg doses and 40-160 mg in multiple daily doses.

**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 at least 60%. The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when ACCUPRIL tablets are administered during a high-fat meal.

**Distribution:** Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

**Metabolism:** Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of ACCUPRIL, there is an effective accumulation half-life of quinaprilat

of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose.

**Elimination:** Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose. It 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.

**Renal Impairment:** In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic haemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. A study in 20 patients with renal impairment (creatinine clearance 12-119 mL/min/1.73 m<sup>2</sup>) showed alterations in both quinapril and quinaprilat pharmacokinetics. The C<sub>max</sub> and AUC for quinapril were greater in patients with renal impairment and the elimination half-life tended to be longer. However, these changes were small and probably not clinically important. The pharmacokinetic data for quinaprilat were markedly different. C<sub>max</sub>, AUC and the elimination half-life all increased as renal impairment became greater. When the creatinine clearance was below 40 mL/min/1.73 m<sup>2</sup>, trough levels of quinaprilat were markedly increased. The elimination half-life increased from 2 to 4 hours as creatinine clearance fell from 120 to 40 mL/min/1.73 m<sup>2</sup> and increased further to 12-14 hours when creatinine was 12 mL/min/1.73 m<sup>2</sup>. Thus, if a person has a creatinine clearance below 40 mL/min/1.73 m<sup>2</sup>, then it is likely that quinaprilat will accumulate and quinapril therapy should be started at a low dose and gradually titrated upward. If creatinine clearance is greater than 40 mL/min/1.73 m<sup>2</sup>, quinapril and quinaprilat are unlikely to accumulate.

**Hepatic Impairment:** The elimination half-life of quinapril was found to have doubled in patients with hepatic impairment from alcoholic cirrhosis when compared to age-matched healthy volunteers. This indicates that liver metabolism is an important facet of quinapril metabolism. There was no alteration in the elimination half-life of quinaprilat probably because renal excretion is its principal route of elimination. The plasma quinaprilat levels, were, however, lower than in matched controls. These results suggested that not only the rate but the extent of the conversion of quinapril to quinaprilat was impaired. Particularly in patients with severe hepatic insufficiency there may be a reduction in efficacy of quinapril due to failure of conversion to the active metabolite. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril.

**Cardiac Impairment:** The presence of mild to moderate congestive heart failure *per se* appears to have minimal effect on the pharmacokinetics of quinaprilat, except in so far that congestive heart failure may be associated with renal failure. Dosing of quinapril in patients with congestive heart failure should be based on their renal function.

**Elderly Patients:** Elimination of quinaprilat is reduced in elderly patients (≥65 years); this reduction is attributable to a decrease in renal function (see **DOSAGE AND ADMINISTRATION**) and not to age itself.

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

## Indications

### Hypertension

ACCUPRIL is indicated for the treatment of essential hypertension. ACCUPRIL is effective as monotherapy or concomitantly with diuretics and beta-blockers in patients with hypertension.

### Congestive Heart Failure

ACCUPRIL is effective in the treatment of congestive heart failure when given concomitantly with a diuretic and/or digoxin.

## Contraindications

ACCUPRIL is contraindicated in:

- Patients who are hypersensitive to this product.
- Patients with history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor.
- Severe renal artery stenosis.
- Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes. These patients are likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore not be used. In such patients, the use of either alternative antihypertensive drugs or alternative membranes (eg. cuprophane or polysulphone PSF) for haemodialysis is recommended.
- 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 (eg. 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**

Hypotension may occur in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertensive patients but is a possible consequence of use in patients with impaired renal function, in salt/volume depleted patients such as patients with renovascular hypertension, vomiting or diarrhoea, those treated vigorously with diuretics, or patients undergoing dialysis (see **PRECAUTIONS, Drug Interactions** and **ADVERSE EFFECTS**). In patients with severe congestive heart failure with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive

azotaemia, but rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. In all high risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Patients already receiving a diuretic when ACCUPRIL is initiated can develop symptomatic hypotension. In these patients it is important, if possible, to stop the diuretic for two to three days before starting ACCUPRIL. If blood pressure is not controlled with ACCUPRIL alone, the diuretic should be resumed. If it is not possible to withdraw diuretic therapy, begin ACCUPRIL at a low initial dose.

### **Anaphylactoid Reactions during 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.

### **Anaphylactoid Reactions during LDL Apheresis**

Patients undergoing low-density lipoprotein apheresis with dextran-sulfate absorption when treated concomitantly with an ACE inhibitor, have reported anaphylactoid reactions.

### **Anaphylactoid Reactions during 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 either alternative antihypertensive drugs or alternative membranes for haemodialysis is recommended.

### **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 ACCUPRIL, 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 20% of patients. These increases were usually reversible upon discontinuation of the ACE inhibitor. ACE inhibitors should not be used in patients with known or suspected renal artery stenosis (see **CONTRAINDICATIONS**). When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

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 quinapril (see **DOSAGE AND ADMINISTRATION**). These patients' dosage should be titrated upwards based upon therapeutic response, and renal function should be closely monitored although initial studies do not indicate that quinapril produces further deterioration in renal function.

In people with a creatinine clearance <40 mL/min/1.73 m<sup>2</sup>, quinaprilat did accumulate but not as much as would be suggested by the increased half life (2.2 hours to 12 hours) implying that alternative methods of removal become important.

Some hypertensive or heart failure patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine, which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**). If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of renal function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium-sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with a non-steroidal anti-inflammatory drug. Evaluation of hypertensive patients should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

### **Impaired Liver Function**

Hepatitis or hepatic failure have been rarely seen in clinical trials with quinapril, however, hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with other ACE inhibitors in patients with or without

pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug. In patients with hepatic impairment from alcoholic cirrhosis, it has been shown that the half-life of quinapril was doubled in comparison to age-matched controlled volunteers. This indicates that liver metabolism is an important facet of quinapril metabolism. There was no alteration in the half-life of quinaprilat probably because renal excretion is its principal method of removal. The plasma quinaprilat levels were, however, lower than matched controls. The results suggested that not only the rate but the extent of the conversion of quinapril to quinaprilat were impaired. Particularly in patients with severe hepatic insufficiency there may be a reduction in efficacy of quinapril due to failure of conversion to the active metabolite.

Quinapril when combined with a diuretic 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.

### **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 which 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.

### **Hyperkalaemia and Potassium-sparing Diuretics**

ACE inhibitors decrease the formation of angiotensin II, which results in decreased production of aldosterone and an increase in serum potassium levels (>5.5 mEq/L). Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium sparing diuretics or potassium supplements and/or consuming potassium containing salt substitutes. Diabetics, and elderly patients particularly, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may co-exist with hyperkalaemia. It

is recommended that patients undergoing ACE inhibitor treatment should have serum electrolytes (including potassium, sodium and urea) measured from time to time (see **PRECAUTIONS** and **Interactions**). This is more important in patients taking diuretics.

### **Neutropenia/Agranulocytosis**

Agranulocytosis and bone marrow depression (including leucopenia/neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leucopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine  $\geq 180 \mu\text{mol/L}$ ) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

### **Foetal/Neonatal Morbidity and Mortality**

See **PRECAUTIONS, Use in Pregnancy (Category D)**.

### **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, 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 1-3 months despite continued treatment.

### **Surgery/Anaesthesia**

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

## **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.

## **Carcinogenicity, Mutagenesis, Impairment of Fertility**

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 man 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 toxicological studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleous test with mice, *in vitro* chromosome aberration with V79 cultured lung cells and an *in vivo* cytogenetic study with rat bone marrow. 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, ACCUPRIL is contraindicated in pregnancy (see **CONTRAINDICATIONS**). Pregnancy should be excluded before starting treatment with ACCUPRIL 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.

There are no adequate and well controlled studies of ACCUPRIL in pregnant women but foetotoxicity is well documented in animal models. Data, however, show that ACCUPRIL crosses the human placenta.

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.

Post-marketing experience with all ACE inhibitors suggest that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have been associated with foetal death *in utero*. Adverse effects appear to be most likely in the second and third trimesters.

Infants exposed to ACE inhibitors during pregnancy may be at an increased risk for malformations of the cardiovascular system and central nervous system. 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. Patients and physicians should be aware, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If such complications occur, attention should be directed toward support of blood pressure and renal perfusion. Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

### **Use in Lactation**

ACE inhibitors, including quinapril, are secreted in human milk to a limited extent. Because of the potential for serious reactions in nursing infants, ACCUPRIL should not be given to a nursing 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 relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no

overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

### **Use in Children**

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

### **Effects on Ability to Drive and use Machines**

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

## **Interactions**

### **Concomitant Diuretic Therapy**

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients on diuretics, especially those on recently instituted diuretic therapy or in those with intravascular volume depletion, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of ACCUPRIL should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised (see **DOSAGE AND ADMINISTRATION**).

### **Agents Increasing Serum Potassium**

ACCUPRIL can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant therapy of an ACE inhibitor with a potassium-sparing diuretic (eg. spironolactone, triamterene, or amiloride), potassium supplement, or potassium-containing salt substitute can increase the risk of hyperkalaemia. Therefore if co-administration is indicated they should be used with caution and patient's serum potassium should be monitored frequently.

### **Tetracycline and Other Drugs That Interact With Magnesium**

Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if co-prescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

## **Lithium**

Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

## **Nonsteroidal Anti-inflammatory Drugs**

Nonsteroidal anti-inflammatory drugs with prostaglandin synthetase inhibitory properties (e.g. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors.

## **Agents Affecting Sympathetic Activity**

Agents affecting sympathetic activity (eg. 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.

## **Other Agents**

Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by ACCUPRIL co-administration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

## **Adverse Effects**

### **Hypertension**

ACCUPRIL 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. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for one year or more.

Adverse experiences were usually mild and transient in nature. Discontinuation of therapy because of adverse events was required in 4.7% of patients in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

### Adverse Events in Placebo-Controlled Trials

	Accupril (n=1563) Incidence (Discontinuance)	Placebo (n=579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea and/or Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

### Heart Failure

ACCUPRIL has been evaluated for safety in 1222 ACCUPRIL treated patients. Of these, 632 patients participated in controlled trials. In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 6.8% of patients with congestive heart failure.

Adverse experience probably or possibly related or of unknown relationship to therapy occurring in 1% or more of the 585 patients in placebo-controlled congestive heart failure trials who were treated with ACCUPRIL are shown below.

	Accupril (N=585) Incidence (Discontinuance)	Placebo (N=295) Incidence (Discontinuance)
Dizziness	7.7 (0.7)	5.1 (1.0)
Coughing	4.3 (0.3)	1.4
Hypotension	2.9 (0.5)	1.0
Fatigue	2.6 (0.2)	1.4
Nausea and/or Vomiting	2.4 (0.2)	0.7
Chest Pain	2.4	1.0
Dyspnoea	1.9 (0.2)	2.0
Diarrhoea	1.7	1.0
Headache	1.7	1.0 (0.3)
Myalgia	1.5	2.0
Rash	1.4 (0.2)	1.0
Back Pain	1.2	0.3

## Cough

See **PRECAUTIONS**.

## Hypertension and/or Heart Failure

Clinical adverse experiences probably, possibly or definitely related, or of uncertain relationship to therapy occurring in 0.5% to  $\leq 1.0\%$  (except as noted) of the patients with congestive heart failure or hypertension treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N=4847) and less frequent, clinically significant events seen in clinical trials or post-marketing experience listed by body system include:

- Body as a Whole: anaphylactoid reaction, photosensitivity reaction.
- Cardiovascular: palpitations, vasodilatation, tachycardia, heart failure, hyperkalaemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances, cardiogenic shock, syncope.
- Gastrointestinal: flatulence, dry mouth or throat, constipation, gastrointestinal haemorrhage, pancreatitis, abnormal liver function tests, hepatitis.
- Haematological: thrombocytopenia, haemolytic anaemia, agranulocytosis.
- Nervous/psychiatric: somnolence, vertigo, nervousness, depression.
- Integumentary: increased perspiration, pruritus, exfoliative dermatitis, dermatopolymyositis, alopecia, pemphigus, rash.
- Urogenital: urinary tract infection, impotence, acute renal failure, worsening renal failure.
- Respiratory: eosinophilic pneumonitis.
- Congenital, familial, and genetic disorders: see **CONTRAINDICATIONS** and **PRECAUTIONS**, Use in **Pregnancy**.
- Other: amblyopia, oedema (peripheral and generalised), arthralgia pharyngitis.
- Angioedema: angioedema (0.1%) was reported in patients receiving ACCUPRIL. Angioedema associated with laryngeal oedema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately (see **PRECAUTIONS**).

## Laboratory Findings

**Haematology:** see **PRECAUTIONS**.

**Hyperkalaemia:** see **PRECAUTIONS**.

**Creatinine and Blood Urea Nitrogen:** Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of the patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often reversed on continued therapy.

## Dosage and Administration

### Hypertension in Adults

#### *Monotherapy*

The recommended initial dosage of ACCUPRIL in patients not on diuretics is 10 mg once daily. Depending upon clinical response, the patient's dosage may be titrated (by doubling the dose) to a maintenance dosage of 20 mg to 40 mg/day given as a single dose or divided into two doses. Generally dosage adjustments should be made at intervals of four weeks. Long-term control is maintained in most patients with a single daily dosage regimen. Patients have been treated with dosages of ACCUPRIL up to 80 mg/day.

#### *Concomitant Diuretics*

In patients who are also being treated with a diuretic, the initial dosage of ACCUPRIL should not exceed 5 mg in order to determine if excess hypotension will occur. The dosage should subsequently be titrated (as described above) to the optimal response.

#### *Renal Impairment*

Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. Recommended starting dosages based on clinical and pharmacokinetic data from patients with renal impairment are as follows:

Creatinine Clearance	Maximum Recommended Initial Dosage
>60 mL/min	10 mg
30-60 mL/min	5 mg
10-30 mL/min	2.5 mg
<10 mL/min	Insufficient data for Dosage recommendation

Age alone does not appear to affect the efficacy or safety profile of quinapril. Therefore, the recommended initial dosage of quinapril in elderly patients is 10 mg given once daily followed by titration to the optimal response.

## **Congestive Heart Failure in Adults**

The recommended initial dose in patients with congestive heart failure is a single 5 mg dose following which the patient should be monitored closely for symptomatic hypotension. After this, patients should be titrated to an effective dose (up to 40 mg/day) given in 1 or 2 doses with concomitant diuretic or cardiac glycoside therapy. Patients are usually maintained effectively on doses of 10 to 20 mg/day given with concomitant therapy.

## **Children**

Not recommended for children.

## **Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatraemia**

Pharmacokinetic data indicate that quinapril elimination is dependent on level of renal function in patients with heart failure and renal impairment. The recommended initial dose of ACCUPRIL is 5 mg in patients with creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance of 10 to 30 mL/min. There is insufficient data for dosage recommendation in patients with creatinine clearance less than 10 mL/min (see **DOSAGE AND ADMINISTRATION, Congestive Heart Failure, PRECAUTIONS and INTERACTIONS**).

## **Overdosage**

The oral LD<sub>50</sub> of quinapril range from 1440 to 4280 mg/kg in mice and rats.

No specific information is available on the treatment of overdosage with quinapril.

The most likely clinical manifestation would be symptoms attributable to severe hypotension. Survival has been reported in a 24-year-old male who presented with acute renal failure after intentionally ingesting 150 to 200 mg of quinapril. The patient recovered without haemodialysis.

Treatment is symptomatic and supportive, consistent with established medical care. Hypotension would normally be treated by intravenous volume expansion, such as an infusion of normal saline. Persistent hypotension should be treated by established procedures. 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 (eg. manoeuvres to change pH of the urine) that might accelerate elimination of quinapril and its metabolites.

Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Because the hypotensive effect of quinapril is achieved through vasodilation and effective hypovolaemia, it is reasonable to treat quinapril overdose by infusion of normal saline solution.

## Presentation

**Accupril 5 mg tablets** are reddish-brown, oval, biconvex film-coated tablets with bisecting score on both sides and debossing “5” on both sides in opposite direction, blister pack of 30.

**Accupril 10 mg tablets** are reddish-brown, triangular, biconvex film-coated tablets with bisecting score on both sides and debossing “10” on one side, blister pack of 30.

**Accupril 20 mg tablets** are reddish-brown, round, biconvex film-coated tablets with bisecting score on both sides and debossing “20” on one side, blister pack of 30.

## Pharmaceutical Precautions

Store below 25°C.

## Medicine Classification

Prescription medicine.

## Package Quantities

Blister packaging of 30 tablets (5 mg, 10 mg and 20 mg).

## Name and Address

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NEW ZEALAND

Toll Free Number: 0800 736 363

## Date of Preparation

24 November 2010

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\* Please note changes in Data Sheet