PRODUCT MONOGRAPH

ACCUPRIL*

(Quinapril Hydrochloride)

5, 10, 20 and 40 mg Tablets

Angiotensin Converting Enzyme Inhibitor

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ACCUPRIL®

(Quinapril Hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet: 5,10, 20 and 40 mg	candelilla wax, crospovidone, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, magnesium carbonate, magnesium stearate, polyethylene glycol, synthetic red iron oxide and titanium dioxide

INDICATIONS AND CLINICAL USE

Hypertension

ACCUPRIL (quinapril hydrochloride) is indicated in the treatment of essential hypertension. It is usually administered in association with other drugs, particularly thiazide diuretics.

The safety and efficacy of ACCUPRIL in renovascular hypertension has not been established; therefore, use in this condition is not recommended.

Congestive Heart Failure

ACCUPRIL is indicated in the treatment of congestive heart failure as adjunctive therapy when added to diuretics and/or digitalis glycosides.
Treatment with ACCUPRIL should be initiated under close medical supervision.

Geriatrics (>65 years of age)

Of the total number of subjects in clinical studies of ACCUPRIL, 21% were ≥65 years old. (There was no distinction between patients >65 or >75 years.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience did not identify differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (<18 years of age)

The safety and effectiveness of ACCUPRIL in children have not been established, therefore use in this age group is not recommended.

CONTRAINDICATIONS

ACCUPRIL is contraindicated in:

- Patients who are hypersensitive to the drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme (ACE) inhibitor (see WARNINGS AND PRECAUTIONS, **General**, **Head and Neck Angioedema**).
- Combination with sacubitril/valsartan due to increased risk of angioedema.
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see WARNINGS AND PRECAUTIONS, **Special Populations**, **Pregnant Women** and ADVERSE REACTIONS).
- Nursing women (see WARNINGS AND PRECAUTIONS, **Special Populations, Nursing Women**).
- Combination with aliskiren-containing medicines in patients with:
    - diabetes mellitus (type 1 or type 2),
    - moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2),
    - hyperkalemia (> 5mMol/L) or

- congestive heart failure who are hypotensive (see WARNINGS AND PRECAUTIONS, **Dual blockade of the Renin-Angiotensin System (RAS)** and **Renal Impairment**, and DRUG INTERACTIONS, **Aliskiren-containing medicines** and **Angiotensin receptor blockers (ARBs) or other ACE inhibitors**).

- Combination with angiotensin receptor blockers (ARBs) or other ACE inhibitors in patients with:
  - diabetes with end organ damage,
  - moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73m^2),
  - hyperkalemia (> 5mMol/L) or
  - congestive heart failure who are hypotensive (see DRUG INTERACTIONS, **Angiotensin receptor blockers (ARBs) or other ACE inhibitors**).
- Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency as ACCUPRIL contains lactose (see WARNINGS AND PRECAUTIONS, **Sensitivity/Resistance**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, ACCUPRIL should be discontinued as

General

Head and Neck Angioedema

Head and neck angioedema has been reported in patients treated with ACCUPRIL. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ACCUPRIL should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition

generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy (including but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients taking a concomitant mTOR inhibitor (e.g. temsirolimus), DPP-4 inhibitor (e.g. sitagliptin) or neutral endopeptidase (NEP) inhibitor may be at increased risk for angioedema. Caution should be used when either initiating ACE inhibitor therapy in patients already taking a mTOR, DPP-4 inhibitor or NEP inhibitor or vice versa (see DRUG INTERACTIONS).

Patients with a history of angioedema related or unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. 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.

Cardiovascular

Dual blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as ACCUPRIL, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including acute renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe kidney insufficiency (GFR < 60

mL/min/1.73 m^2). Therefore, the use of ACCUPRIL in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including ACCUPRIL, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia. Administration should be limited to individually defined cases with close monitoring of renal function and blood potassium levels (see CONTRAINDICATIONS).

Hypotension

Symptomatic hypotension has occurred after administration of ACCUPRIL, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (See ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ACCUPRIL should be started under close medical supervision (see DOSAGE AND ADMINISTRATION). Such patients should be followed closely for the first weeks of treatment and whenever the dose of ACCUPRIL is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute failure and/or death.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. 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. However, lower doses of ACCUPRIL and/or reduced concomitant diuretic therapy should be considered.

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Endocrine and Metabolism

Hyperkalemia

Elevated serum potassium (>5.7 mMol/L) was observed in approximately 2% of patients receiving ACCUPRIL. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in <0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia, potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs known to raise serum potassium levels. Because of the risk of hyperkalemia it is advised that combination therapy be initiated with caution and the patient's serum potassium levels be closely monitored (see WARNINGS AND PRECAUTIONS, **Monitoring and Laboratory Test**, ***Hyperkalemia***, ADVERSE REACTIONS, and DRUG INTERACTIONS, Agents Increasing Serum Potassium, **Trimethoprim-containing products**).

Hyponatraemia and SIADH

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with other ACE inhibitors. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Hypoglycemia and Diabetes

ACE inhibitors may reduce insulin resistance and may lead to hypoglycemia in diabetic patients on insulin or oral hypoglycemic agents; closer monitoring of diabetic patients may be required.

Hematologic

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Agranulocytosis did occur during ACCUPRIL treatment in 1 patient with a history of neutropenia during previous captopril therapy. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Hepatic

Patients with Impaired Liver Function

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.

Elevations of liver enzymes and/or serum bilirubin have been reported for ACCUPRIL (see ADVERSE REACTIONS). Should the patient receiving ACCUPRIL experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of ACCUPRIL should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ACCUPRIL should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

ACCUPRIL (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. The metabolism of quinapril to quinaprilat is normally dependent upon hepatic esterase. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril.

Immune

Anaphylactoid Reactions during Membrane Exposure

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during LDL Apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding the ACE inhibitor therapy prior to each apheresis.

Anaphylactoid Reactions during Desensitization

There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge to an ACE inhibitor.

Nitritoid Reactions-Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ACCUPRIL (see DRUG INTERACTIONS).

Neurologic

Driving and Operating Machinery

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

Peri-Operative Considerations

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Renal

Renal Impairment

The use of ACE inhibitors, including ACCUPRIL, with ARBs or aliskiren-containing drugs is contraindicated in patients with moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73m^2) (see CONTRAINDICATIONS and DRUG INTERACTIONS, **Aliskiren-containing medicines** and **Angiotensin receptor blockers (ARBs) or other ACE inhibitors**).

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the RAAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Use of ACCUPRIL should include appropriate assessment of renal function (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Respiratory

Cough

Cough has been reported with the use of ACE inhibitors, including quinapril. Characteristically, the cough is dry and persistent and usually disappears only after withdrawal or lowering of the

dose of ACCUPRIL. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of the cough.

Sensitivity/Resistance

Due to the presence of lactose, patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency should not take ACCUPRIL (see CONTRAINDICATIONS).

Special Populations

Pregnant Women

Quinapril is contraindicated in pregnancy (see CONTRAINDICATIONS and ADVERSE REACTIONS). ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations have also been reported, following exposure in the first trimester of pregnancy.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function, however;

limited experience with those procedures has not been associated with significant clinical benefit.

If oligohydramnios is observed, a non-stress test (NST), and/or a biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. If concerns regarding fetal well-being still persist, a contraction stress testing (CST) should be considered. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Animal Data: No fetotoxic or teratogenic effects were observed in rats at doses as high as 300 mg/kg/day (180x the maximum daily human dose), despite maternal toxicity at 150 mg/kg/day. Offspring body weights were reduced in rats treated late in gestation and during lactation with doses of ≥25 mg/kg/day. Quinapril hydrochloride was not teratogenic in rabbits; however, maternal and embryo toxicity were seen in some rabbits at 1 mg/kg/day.

No adverse effects on fertility or reproduction were observed in rats at dose levels ≤100 mg/kg/day (60x the maximum daily human dose) (see TOXICOLOGY, Table 4).

Nursing Women

The presence of concentrations of ACE inhibitor has been reported in human milk. The use of ACCUPRIL is contraindicated during breast-feeding (see CONTRAINDICATIONS).

Pediatrics (<18 years of age)

The safety and effectiveness of ACCUPRIL in children have not been established, therefore use in this age group is not recommended.

Geriatrics (>65 years of age)

Of the total number of subjects in clinical studies of ACCUPRIL, 21% were ≥65 years old. (There was no distinction between patients >65 or >75 years.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported

clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Elderly patients exhibited increased area under the plasma concentration time curve 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.

Monitoring and Laboratory Tests

Hematology: Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease (see WARNINGS AND PRECAUTIONS, **Hematologic**, **Neutropenic/Agranulocytisis**).

Hyperkalemia: Patients with renal insufficiency, diabetes mellitus or concomitantly taking agents to treat hypokalemia may be at increased risk of developing hyperkalemia. Serum potassium should be monitored regularly (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, **Endocrine and Metabolism**, **Hyperkalemia**).

***Hyponatraemia*:** (see WARNINGS AND PRECAUTIONS, **Endocrine and Metabolism**, **Hyponatraemia and SIADH**).
It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Creatinine and Blood Urea Nitrogen: Increases (>1.25x the upper limit of normal) in serum creatinine and blood urea nitrogen (BUN) were observed in 2% each of patients treated with ACCUPRIL alone. Increases were more likely to occur in patients receiving concomitant

diuretic therapy than in those on ACCUPRIL alone (see WARNINGS AND PRECAUTIONS, **Renal**, **Renal Impairment**). These increases often reversed on continued therapy. In controlled studies of heart failure, increases in BUN and serum creatinine were observed in 11% and 8%, respectively, of patients treated with ACCUPRIL. Most often, these patients were receiving diuretics with or without digitalis. Use of ACCUPRIL should include appropriate assessment of renal function.

Hepatic: Elevations of liver enzymes and/or serum bilirubin have occurred in patients receiving ACCUPRIL. If a patient receiving ACCUPRIL experience any unexplained symptoms, particularly during the first weeks or months of treatment, a full set of liver function tests and any other investigation should be carried out. Discontinuation of ACCUPRIL should be considered when appropriate. In patients with pre-existing liver abnormalities, baseline liver function tests should be obtained before administration of the drug and response and metabolic effects should be closely monitored (see WARNINGS AND PRECAUTIONS, **Hepatic**, **Patients with Impaired Liver Function**).

ADVERSE REACTIONS

Hypertension

ACCUPRIL (quinapril hydrochloride) monotherapy was evaluated for safety in 2005 hypertensive patients, including 313 elderly patients, enrolled in placebo-controlled clinical trials. There was no increase in the incidence of adverse events (AEs) in elderly patients given the same daily dosages. ACCUPRIL was evaluated for long-term safety in >1100 patients treated for ≥1 year. AEs were usually mild and transient in nature.

The most serious AE was angioedema (0.1%). Renal insufficiency (1 case), agranulocytosis (1 case) and mild azotemia (2 cases in CHF patients) have been reported. Myocardial infarction and cerebrovascular accident occurred, possibly secondary to excessive hypotension in high risk patients (see WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension**).

The most frequent AEs in controlled clinical trials were headache (8.1%), dizziness (4.1%), cough (3.2%), fatigue (3.2%), rhinitis (3.2%), nausea and/or vomiting (2.3%), and abdominal pain (2.0%).
Discontinuation of therapy because of AEs was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled trials.

Congestive Heart Failure (CHF)

Out of the 1108 patients with CHF, 605 (55%) experience ≥1 AE. In controlled clinical trials, 525 of these patients were evaluated for safety. The frequencies of AEs were similar for both sexes as well as for younger (< 65 years) and older (> 65 years) patients.

The most serious non-fatal AEs/reactions were angioedema (0.1%), chest pain of unknown origin (0.8%), angina pectoris (0.4%), hypotension (0.1%) and impaired renal function (see WARNINGS AND PRECAUTIONS, **Renal**, **Renal Impairment**). Myocardial infarct and cerebrovascular accident occurred (see WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension**). Rare cases of eosinophilic pneumonitis have been reported. Hepatitis or hepatic failure have rarely been observed with other ACE inhibitors.

The most frequent AEs in controlled clinical trials were dizziness (11.2%), cough (7.6%), chest pain (6.5%), dyspnea (5.5%), fatigue (5.1%), and nausea/vomiting (5.0%).

Discontinuation due to AEs in controlled clinical trials was required for 41 (8.0%) patients. Hypotension (0.8%) and cough (0.8%) were the most common reasons for withdrawal.

AEs occurring in ≥ 0.5% of 2005 hypertensive patients treated with ACCUPRIL monotherapy and in 525 patients with CHF treated with ACCUPRIL as adjunctive therapy, in controlled clinical trials, are presented in the table below:

Table 1: Adverse Events in Patients (≥ 0.5%) with Hypertension and Congestive Heart Failure in Controlled Clinical Trials (Irrespective of Causal Relationship)
(Page 1 of 2)

	Hypertension[1] % Patients (N=2005)	Congestive Heart Failure[2] % Patients (N=525)
BODY AS A WHOLE		
Chest Pain	1.2	6.5
Fatigue	3.2	5.1
Headache	8.1	3.2
Back Pain	1.3	1.7
Asthenia	1.0	1.7
Peripheral Edema	0.9	1.5
Generalized Edema	0.7	0.2
CARDIOVASCULAR SYSTEM		
Hypotension	1.0	3.4
Angina Pectoris	0.2	2.3
Palpitation	0.4	1.3
Tachycardia	0.2	1.1
Myocardial infarct	-	0.6
Arrhythmia	0.1	0.6
DIGESTIVE SYSTEM		
Nausea and/or vomiting	2.3	5.0
Abdominal pain	2.0	2.5
Diarrhea	1.9	3.4
Dyspepsia	1.9	1.5
Dry mouth or throat	0.4	0.8
MUSCULOSKELETAL SYSTEM		
Myalgia	1.7	2.9

[1] ACCUPRIL monotherapy
[2] ACCUPRIL as adjunctive therapy to diuretic and/or digitalis.

Table 1: Adverse Events in Patients (≥ 0.5%) with Hypertension and Congestive Heart Failure in Controlled Clinical Trials (Irrespective of Causal Relationship)
(Page 2 of 2)

	Hypertension[1] % Patients (N=2005)	Congestive Heart Failure[2] % Patients (N=525)
NERVOUS SYSTEM		
Dizziness	4.1	11.2
Insomnia	1.3	1.1
Paresthesia	1.0	1.3
Nervousness	1.0	0.2
Somnolence	0.9	0.6
Syncope	0.3	0.6
Vertigo	0.4	0.8
Depression	0.6	1.0
RESPIRATORY		
Cough	3.2	7.6
Dyspnea	0.9	5.5
Hemoptysis	-	0.6
Rhinitis	3.2	2.5
SKIN AND APPENDAGES		
Rash	0.6	1.9
Sweating increased	0.8	1.1
Pruritus	0.6	0.4
UROGENITAL SYSTEM		
Impotence	0.5	0.2
SPECIAL SENSES		
Amblyopia	0.3	1.3
Unusual Taste	0.1	0.8
Abnormal Vision	0.1	0.6
Taste Loss	0.2	0.6

1 ACCUPRIL monotherapy
2 ACCUPRIL as adjunctive therapy to diuretic and/or digitalis.

AEs occurring in <0.5% of patients with hypertension or CHF include:

Body as a whole:	Allergy, chill, dehydration, face edema, weight increase
Cardiovascular:	atrial flutter, cerebrovascular accident, heart failure vasodilatation, ventricular tachycardia
Digestive System:	Anorexia, bloody stools, constipation, GI hemorrhage, tongue edema
Hemic and Lymphatic System:	Agranulocytosis, anemia, including hemolytic anemia
Nervous System:	Amnesia, anxiety, arthralgia, confusion
Musculoskeletal System:	Arthritis
Respiratory System:	Asthma, hoarseness
Skin and Appendages:	Dermatitis, eczema, Stevens-Johnson syndrome, urticaria
Urogenital system:	Dysuria, impaired renal function, polyuria
Special senses:	Tinnitus
Laboratory Deviations:	Azotemia, elevated BUN, hematuria, hyperglycemia, WBC decreased

Clinical adverse experiences probably, possibly, or definitely related, or of uncertain relationship to therapy occurring in 0.5% to ≤ 1.0% of the patients treated with quinapril (with or without concomitant diuretic) in controlled or uncontrolled clinical trials and less frequent events seen in clinical trials or post-marketing experience (indicated by a *) included:

Body as a Whole:	Anaphylactoid reaction*; photosensitivity reaction*
Cardiovascular:	Postural hypotension*, syncope*, vasodilation
Congenital and familial/genetic disorders:	Fetal/neonatal injury including: anuria, hypotension, oligohydramnios, skull hypoplasia, reversible or irreversible renal failure, and death (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, **Pregnant Women**)
Gastrointestinal:	Flatulence, pancreatitis*
Hemic and Lymphatic:	Thrombocytopenia*
Integumentary:	Alopecia*, exfoliative dermatitis*, pemphigus*
Urogenital:	Urinary tract infection

Other: Arthralgia, edema (peripheral and generalized), hemolytic anemia*

DRUG INTERACTIONS

Drug-Drug Interactions

Proper name	Reference	Effect	Clinical comment
Agents Affecting Sympathetic Activity	---		Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to ACCUPRIL.
Agents Increasing Serum Potassium	---	Since ACCUPRIL decreases aldosterone production, elevation of serum potassium may occur.	Potassium sparing diuretics such as spironolactone, triamterene or amiloride, potassium supplements or other drugs known to raise serum potassium levels should be given with caution and with frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.
Aliskiren-containing medicines	CT	Dual blockade of the renin-angiotensin-aldosterone system by combining an ACE inhibitor with aliskiren-containing medicines is not recommended since there is an increased risk of hypotension, syncope, stroke, hyperkalemia and changes in renal function, including renal failure.	The use of ACCUPRIL in combination with aliskiren-containing medicines is contraindicated in patients with • diabetes mellitus (type 1 or type 2), • moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2), • hyperkalemia (> 5mMol/L) or • congestive heart failure who are hypotensive It is not recommended in other patients (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, **Dual blockade of the Renin-Angiotensin System (RAS)**)

Proper name	Reference	Effect	Clinical comment
Angiotensin receptor blockers (ARBs) or other ACE inhibitors	CT	Dual blockade of the renin-angiotensin-aldosterone system by combining an ACE inhibitor with ARBs or other ACE~~s~~ inhibitors is not recommended since there is an increased risk of hypotension, syncope, stroke, hyperkalemia and changes in renal function, including renal failure.	The use of ACCUPRIL in combination with ARBs or other ACE inhibitors is contraindicated in patients with • diabetes and end organ damage, • moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2), • hyperkalemia (> 5mMol/L) or • congestive heart failure who are hypotensive. It is not recommended in other patients (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Dual blockade of the Renin-Angiotensin System (RAS)**)
Antidiabetic agents (e.g. insulin, oral hypoglycemic agents, sitagliptin)	CT	ACE inhibitors may reduce insulin resistance and may lead to hypoglycemia in diabetic patients on insulin or oral hypoglycemic agents.	Monitor closely diabetic patients (see WARNINGS AND PRECAUTIONS, **Endocrine and Metabolism, Hypoglycemia and Diabetes**).
		Patients taking concomitant DPP-4 inhibitor therapy may be at increased risk for angioedema.	Caution should be used when either initiating ACE inhibitor therapy in patients already taking a DPP-4 inhibitor or *vice versa* (see WARNINGS AND PRECAUTIONS, **General**, **Head and Neck Angioedema**).
Anti-neoplastic drugs, including cyclophosphamide , methotrexate and mTOR inhibitors (e.g.temsirolimus, everolimus)	C, CT	Patients taking concomitant mTOR inhibitor therapy may be at increased risk for angioedema.	Caution should be used when either initiating ACE inhibitor therapy in patients already taking an mTOR inhibitor or *vice versa* (see WARNINGS AND PRECAUTIONS, **General**, **Head and Neck Angioedema**).
Concomitant Diuretic Therapy	---	Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy.	The possibility of hypotensive effects after the first dose of ACCUPRIL can be minimized by either discontinuing the diuretic or increasing the salt intake (except in patients with heart failure) 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 should be closely observed for several hours following initial dose and until blood pressure has stabilized (see WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension** and DOSAGE AND ADMINISTRATION).

Proper name	Reference	Effect	Clinical comment
Gold	C	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ACCUPRIL (see WARNINGS AND PRECAUTIONS, **Immune**, **Nitritoid Reactions-Gold**).	
Lithium	---	As with other drugs which eliminate sodium, the lithium elimination may be reduced.	The serum lithium levels should be monitored carefully if lithium salts are to be administered.
Neutral endopeptidase inhibitor	---	Patients taking concomitant neutral endopeptidase inhibitor may be at increased risk for angioedema.	Caution should be used when either initiating ACE inhibitor therapy in patients already taking a neutral endopeptidase inhibitor or *vice versa* (see WARNINGS AND PRECAUTIONS, **General**, **Head and Neck Angioedema**).
Non-Steroidal Anti-Inflammatory Drugs (NSAID) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors)	CT	In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including quinapril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ACE inhibitors, including quinapril may be attenuated by NSAIDs.	Monitor renal function periodically in patients receiving quinapril and NSAID therapy.
Other Antihypertensive Agents	CT	The antihypertensive effect of ACCUPRIL is augmented by antihypertensive agents that cause renin release (e.g. diuretics).	
Sirolimus (immune-suppressant mTOR inhibitor)	CT	Organ transplant patients taking concomitant sirolimus therapy may be at increased risk for angioedema.	Caution should be used when either initiating ACE inhibitor therapy in patients already taking sirolimus or *vice versa* (see WARNINGS AND PRECAUTIONS, **Head and Neck Angioedema**).

Proper name	Reference	Effect	Clinical comment
Tetracycline	---	Concomitant administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline in healthy volunteers (by 28-37%) due to the presence of magnesium carbonate as an excipient in the formulation.	This interaction should be considered with concomitant use of ACCUPRIL and tetracycline or other drugs which interact with magnesium.
Trimethoprim-containing products (sulfamethoxazole/trimethoprim)	C	In patients who are elderly or have compromised renal function, co-administration of an ACE inhibitor with sulfamethoxazole/trimethoprim has been associated with severe hyperkalemia, likely due to the hyperkalemic effects of trimethoprim.	Quinapril and trimethoprim-containing products should only be co-administered with caution and with appropriate monitoring of serum potassium.
Other Agents	CT	In single dose pharmacokinetic studies, no important changes in pharmacokinetic parameters were observed when ACCUPRIL was used concomitantly with propranolol, hydrochlorothiazide, digoxin, or cimetidine. No change in prothrombin time occurred when ACCUPRIL and warfarin were given together.	

Legend: C=Case Study; RCS=Retrospective Cohort Study; CT=Clinical Trial; T=Theoretical

Drug-Food Interactions

The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when ACCUPRIL tablets are administered during a high-fat meal. However, no effect on quinapril absorption occurs when taken during a regular meal.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory products/methods have not been established.

Drug-Lifestyle Interactions

Lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosage of ACCUPRIL (quinapril hydrochloride) must be individualized.

Hypertension

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure (BP) elevation and salt restriction. The dosage of other antihypertensive agents being used with ACCUPRIL may need to be adjusted.

Monotherapy:

The recommended initial dose of ACCUPRIL in patients not on diuretics is 10 mg once daily. An initial dose of 20 mg once daily can be considered for patients without advanced age, renal impairment, or concomitant heart failure and who are not volume depleted (see WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension**). Dosage should be adjusted according to BP response, generally at intervals of 2-4 weeks. A dose of 40 mg daily should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring BP just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either 2x daily administration with the same total daily dose, or an increase in dose should be considered. If BP is not controlled with ACCUPRIL alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ACCUPRIL.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ACCUPRIL and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for 2-3 days before beginning therapy with ACCUPRIL to reduce the likelihood of hypotension (See WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension**). If the diuretic cannot be discontinued, an initial dose of 5 mg ACCUPRIL should be used with careful medical supervision for several hours and until BP has stabilized. The dosage of ACCUPRIL should subsequently be titrated (as described above) to the optimal response.

Dosing Adjustment in Renal Impairment: For use in hemodialysis patients, see WARNINGS and PRECAUTIONS, **Anaphylactoid Reactions during Membrane Exposure**. Quinapril should be administered on days when dialysis is not performed.
Starting doses should be reduced according to the following guidelines:

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

Patients should subsequently have dosage titrated (as described above) to the optimal response.

Dosage in the Elderly (>65 years): The recommended initial dosage of ACCUPRIL is 10 mg once daily (depending on renal function), followed by titration (as described above) to the optimal response.

Congestive Heart Failure

ACCUPRIL is indicated as adjunctive therapy to diuretics, and/or cardiac glycosides. Therapy should be initiated under close medical supervision. BP and renal function should be monitored, both before and during treatment with ACCUPRIL, because severe hypotension and, more rarely, consequent renal failure have been reported (see WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension**).

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning

treatment, to reduce the likelihood of hypotension. Serum potassium should also be monitored (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS).

The recommended starting dose is 5 mg once daily, to be administered under close medical supervision to determine the initial effect on BP. After the initial dose, the patient should be observed for ≥2 hours, or until the pressure has stabilized for ≥1 additional hour (See WARNINGS AND PRECAUTIONS, **Cardiovascular**, **Hypotension**). This dose may improve symptoms of heart failure, but increases in exercise duration have generally required higher doses. Therefore, if the initial dosage of ACCUPRIL is well tolerated or after effective management of symptomatic hypotension following initiation of therapy, the dose should then be increased gradually to 10 mg once daily, then 20 mg once daily, and to 40 mg per day given in 2 equally divided doses, depending on the patient's response. The maximum daily dose is 40 mg.

The dose titration may be done at weekly intervals, as indicated by the presence of residual signs or symptoms of heart failure.

Renal Impairment or Hyponatremia: Kinetic data indicate that ACCUPRIL elimination is dependent on the level of renal function. The recommended initial dose of ACCUPRIL is 5 mg in patients with a creatinine clearance of 30- 60 mL/min and 2.5 mg in patients with a creatinine clearance of 10-30 mL/min. There is insufficient data for dosage recommendation in patients with a creatinine clearance <10 mL/min. If the initial dose is well tolerated, ACCUPRIL may be administered the following day as a 2x daily regimen. In the absence of excessive hypotension or significant deterioration of renal function, the dose may be increased at weekly intervals based on clinical and hemodynamic response (See WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

OVERDOSAGE

No data are available regarding overdosage with ACCUPRIL. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should be normally treated by intravenous volume expansion with 0.9% sodium chloride. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ACCUPRIL (quinapril hydrochloride) is a nonpeptide, nonsulphydryl inhibitor of angiotensin converting enzyme (ACE), which is used in the treatment of hypertension.

ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II. After absorption, quinapril is rapidly de-esterified to quinaprilat (quinapril diacid), its principal active metabolite. Its primary mode of action is to inhibit circulating and tissue ACE, thereby decreasing vasopressor activity and aldosterone secretion. Although the decrease in aldosterone is small, it results in a small increase in serum K^+ (see WARNINGS AND PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Although ACCUPRIL had antihypertensive activity in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than non-black patients.

ACE is identical to kininase II. Thus, quinapril may interfere with the degradation of bradykinin, a potent peptide vasodilator. However, it is not known whether this system contributes to the therapeutic effects of ACCUPRIL.

In animal studies, the antihypertensive effect of quinapril outlasts its inhibitory effect on circulating ACE. Tissue ACE inhibition more closely correlates with the duration of antihypertensive effects and this may be related to enzyme binding characteristics.

Pharmacodynamics

Hypertension

Administration of 10-40 mg of ACCUPRIL to patients with essential hypertension results in a reduction of both sitting and standing BP with minimal effect on heart rate. Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2-4 hours after dosing. Achievement of maximum BP lowering effects may require 2 weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained throughout the 24-hour dosing interval in most patients. While the dose response relationship is relatively flat, a dose of 40 mg was somewhat more effective at trough than 10-20 mg, and 2x daily dosing tended to give a somewhat lower BP than 1x daily dosing with the same total daily dose. The antihypertensive effect of ACCUPRIL was maintained during long-term therapy with no evidence of loss of effectiveness.

Hemodynamic assessments in patients with essential hypertension indicate that BP 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 and cardiac index. There was an increase in renal blood flow which was not significant. Little or no change in glomerular filtration rate (GFR) or filtration fraction was observed.
Quinapril has been shown to reduce microalbuminuria in patients with essential hypertension independently of changes in systemic BP.

When ACCUPRIL is given together with thiazide-type diuretics, the antihypertensive effects are approximately additive.

Congestive heart failure

Administration of ACCUPRIL to patients with congestive heart failure (CHF) reduces peripheral vascular resistance, systolic and diastolic BP, pulmonary capillary wedge pressure, and increases cardiac output. The onset of effects was observed within 1 hour and maximal effects occurred at 1.25- 4 hours after administration of ACCUPRIL. Peak hemodynamic effects correlated well with peak plasma levels of quinaprilat (1- 4 hours after administration).

Exercise tolerance was improved with ACCUPRIL therapy.
The effect of ACCUPRIL on survival in patients with heart failure has not been evaluated.

Pharmacokinetics

Following oral administration of ACCUPRIL, peak plasma concentrations of quinapril occur within 1 hour. Based on the recovery of quinapril and its metabolites in urine, the extent of absorption is ≥60%. Following absorption, quinapril is de-esterified to its major active metabolite, quinaprilat (quinapril diacid) a potent ACE inhibitor, and to minor inactive metabolites. Quinapril has an apparent half-life in plasma of approximately 1 hour. Peak plasma quinaprilat concentrations occur approximately 2 hours after an oral dose of ACCUPRIL. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of approximately 3 hours. Quinaprilat has an elimination half-life in plasma of approximately 2 hours with a prolonged terminal phase of 25 hours. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

Pharmacokinetic studies in patients with end-stage renal disease on chronic hemodialysis or continuous ambulatory peritoneal dialysis indicate that dialysis has little effect on the elimination of quinapril and quinaprilat.

The disposition of quinapril and quinaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until creatinine clearance is ≤60 mL/min. With creatinine clearance <60 mL/min, peak and trough quinaprilat concentrations increase, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat may be reduced in elderly patients (>65 years) and in those with heart failure; this reduction is attributable to decrease in renal function (see DOSAGE and ADMINISTRATION). Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril.

The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when ACCUPRIL tablets are administered during a high-fat meal. However, no effect on quinapril absorption occurs when taken during a regular meal.

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

Special Populations and Conditions

Geriatrics:
Therapeutic effects appear to be the same for elderly (>65 years of age) and younger adult patients given the same daily dosages, with no increase in AEs in elderly patients.

Race:
The antihypertensive effect of ACE inhibitors is generally lower in black than in non-black patients.

STORAGE AND STABILITY

Store at controlled room temperature, 15-30^{o}C. Protect from moisture. Dispense in well-closed containers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ACCUPRIL (quinapril hydrochloride) tablets are supplied as follows:

ACCUPRIL 5 mg: Contains 5 mg quinapril per tablet. Brown, film-coated, elliptical tablets, debossed "PD 527" on one side and "5" on the other side. Bottles of 90 tablets.

ACCUPRIL 10 mg: Contains 10 mg quinapril per tablet. Brown, film-coated, triangular tablets, debossed "PD 530" on one side and "10" on the other side. Bottles of 90 tablets.

ACCUPRIL 20 mg: Contains 20 mg quinapril per tablet. Brown, film-coated, round tablets, debossed "PD 532" on one side and "20" on the other side. Bottles of 90 tablets.

ACCUPRIL 40 mg: Contains 40 mg quinapril per tablet. Brown, film-coated, elliptical tablets, debossed "PD 535" on one side and "40" on the other side. Bottles of 90 tablets.

Composition

ACCUPRIL tablets contain 5 mg, 10 mg, 20 mg or 40 mg quinapril per tablet (as the hydrochloride salt). Each tablet also contains candelilla wax, crospovidone, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, magnesium carbonate, magnesium stearate, polyethylene glycol, synthetic red iron oxide and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

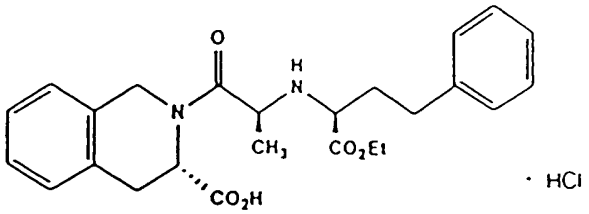
Proper Name: Quinapril Hydrochloride

Chemical Name: [3S-[2[R*(R*)],3R*]] 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid monohydrochloride

Molecular Formula: $C_{25}H_{30}N_2O_5.HCl$

Molecular Weight: 474.98

Molecular Structure:



Description: Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents. The pH of a 1% solution in distilled water is 2.5.

Solubility:

Solvent	% w/v solubility at RT
Water	>10
0.1N HCl	>10
Methanol	>5
95% Ethanol	>5
Acetone	>5
Chloroform	>5
PEG 400	>10

	Propylene Glycol	>10

Dissociation Constants: $pK_{a1} = 2.8$

$pK_{a2} = 5.4$

Partition Coefficients:	**Medium**	**Log-P**
	0.1N HCl	0.86
	0.05M phosphate buffer, pH 2.5	0.68
	0.05M phosphate buffer, pH 4.0	1.35
	0.05M phosphate buffer, pH 7.4	0.33

Melting Range: Melts with decomposition, 108-115°C

DETAILED PHARMACOLOGY

Mechanism of Action

In Vitro Studies: Quinapril was shown to be an inhibitor of angiotensin converting enzyme (ACE) in both plasma and tissue. In assays utilizing human plasma as sources of ACE, the diacid form of quinapril (quinaprilat) exhibited greater inhibition of ACE activity than quinapril (6.4×10^{-10}M and 8.4×10^{-8}M, respectively). In rabbit and rat aortic strips, quinapril (10^{-7}M , 10^{-5}M) specifically suppressed the contractile responses elicited by angiotensin I (50% contraction at approximately 10^{-7}M and 10^{-6}M angiotensin I, respectively), but had no effect on contractions induced by angiotensin II and potassium chloride.

In Vivo Studies: Following oral dosing of quinapril, captopril or enalapril (0.1-3 mg/kg) to conscious normotensive rats, plasma ACE inhibition was assessed *in vivo* by the decrease in pressor response to intravenous (IV) angiotensin I, angiotensin II, norepinephrine and bradykinin. Quinapril produced a dose-dependent reduction (44% at 0.1 mg/kg, 81% at 0.3 mg/kg) of angiotensin I (0.32 µg/kg IV) pressor response and potentiated the response to bradykinin (154% after 0.3 mg/kg quinapril), but had no effect on angiotensin II and norepinephrine responses. Quinapril was equipotent to captopril and enalapril, but had a longer

duration of action than captopril. In the conscious dog, oral administration of quinapril (0.1-3 mg/kg) resulted in plasma ACE inhibition comparable to that of enalapril and captopril.

In human subjects, quinapril at single oral doses of 10-20 mg/day produced 95-100% inhibition of plasma ACE activity at 0.5 hour postdose, with >80% inhibition persisting at 24 hours postdose. Multiple oral doses of quinapril to humans for 12-weeks (20-80 mg/day) confirmed the inhibitory effect on plasma ACE and showed that it produces corresponding decreases in angiotensin II with significant increases in plasma renin activity. Once or 2x daily dosing did not alter the results.

TOXICOLOGY

Acute Toxicity

The acute oral (PO) and intravenous (IV) toxicity of quinapril are summarized in Table 2.

Table 2: Acute Toxicity of Quinapril

Species	Sex	Route of Administration	Median Lethal Dose(mg/kg)
Mouse	Male	PO	1492-2150
	Female	PO	1440-2005
	Male	IV	504
	Female	IV	523
Rat	Male	PO	4280
	Female	PO	3541
	Male	IV	158-300
	Female	IV	108-273
Dog	Male & Female	PO	> 400

Quinapril showed a low order of acute toxicity. Clinical signs of toxicity in both mice and rats were depression or hypoactivity, prostration and ataxia. Peak mortality occurred within 24 hours in oral studies and within 15 minutes in IV studies. Asymptomatic oral dose levels were 500 mg/kg in mice and 1000 mg/kg in rats.

In the dog study, escalating oral doses of 50-400 mg/kg were given over 13-consecutive days. Vomiting occurred after doses of ≥150 mg/kg. BPs decreased with increasing dose. At 400 mg/kg, the female had elevated creatinine and blood urea nitrogen (BUN) levels, decreased sodium and chloride levels, and granular casts in the urine. Gastric erosions and ulcers were seen in both animals and renal tubular dilatation was noted in the female.

The results of quinapril toxicity from subacute, chronic, reproductive, genetic, and carcinogenicity studies are given in Tables 3-7, respectively. Table 8 summarizes the results of toxicity studies with quinaprilat, the major active metabolite of quinapril.

Table 3: Subacute Toxicity Studies of Quinapril

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Results
Mouse	2	10	PO	VC[1], 125,250, 500, 750	One drug-related death at 750 mg/kg; reduced food consumption and body weight gain. MTD[2] about 500 mg/kg.
Mouse	13	10	PO	VC, 50, 125, 250, 500	Body weight gain suppression, decreases in heart weight, hyperplasia of juxtaglomerular apparatus (JGA). MTD between 50 and 125 mg/kg.
Rat	2	5	PO	VC, 200, 400, 800, 1200	Deaths at 400, 800, and 1200 mg/kg; salivation, reduced food consumption, body weight gain suppression, pulmonary, renal, and gastric lesions.
Rat	2	10	PO	UC[1], VC, 100, 400, 800	Deaths at 400 and 800 mg/kg; respiratory signs, salivation, increased BUN, decreased RBC, Hgb, and Hct; increased liver weights, decreased heart weights; pulmonary edema and focal gastric erosions. MTD was between 400 and 800 mg/kg
Rat	13	12	PO	UC, VC, 50, 250, 500	Deaths at 250 and 500 mg/kg; salivation; slightly increased BUN, CPK, and LDH; decreased RBC, Hct, and Hgb; decreased heart weight, pulmonary and gastric lesions at ≥250 mg/kg; increased renin granules in JG cells. MTD between 50 and 250 mg/kg.
Dog	2	2	PO	VC, 25, 125, 250 (125 b.i.d.)	No deaths; emesis, mild focal erosions and inflammation of the stomach at 125 mg/kg. MTD estimated as 250 mg/kg.
Dog	13	3	PO	VC, 25, 125, 250 (125 b.i.d.)	Sporadic emesis and anorexia; mild to moderate reversible increase in BUN and mild depression of RBC, Hct, Hgb at 250 mg/kg; focal gastric erosions at ≥125 mg/kg, increases in renin granules in JG cells; hypertrophy and hyperplasia of JGA. MTD was between 25 and 125 mg/kg.

[1] VC = Vehicle Control; UC = Untreated Control.
[2] MTD = Maximum Tolerated Dose; RBC = red blood cell count; Hgb = hemoglobin; Hct = hematocrit; CPR = creatine phosphokinase; LDH = lactate dehydrogenase; JG = juxtaglomerular apparus; BUN = blood urea nitrogen.

Table 4: Chronic Toxicity Studies of Quinapril

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Results
Rat	57[1]	30	PO	UC[2], VC[2], 10, 50, 100	No drug-related deaths; transient post-dose salivation, body weight gain suppression, increased BUN, decreased glucose, increased plasma renin level, decreased heart weight, JGA hypertrophy and hyperplasia with increased granules; degenerative changes in kidneys.
Dog	52	4	PO	VC, 10, 50, 100	No deaths; elevation of plasma renin and liver enzyme levels, focal areas of chronic active inflammation in the liver at 100 mg/kg; gastric erosion at 50 mg/kg, and hypertrophy/hyperplasia of renal JGA.

[1] 52 weeks treatment plus 4 weeks without treatment for some animals

[2] UC = Untreated Control; VC = Vehicle Control; BUN = blood urea nitrogen; JGA = juxtaglomerular apparatus.

Table 5: Reproductive Toxicology Studies of Quinapril

Species	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Duration of Dosing	Results
Fertility:					
Rat	12 Male 24 Female	PO	VC[1], 10, 50, 100	Males-60 days prior to mating Females-14 days prior to mating until weaning of offspring	No effects on fertility, no adverse effects on F_1offspring parameters, and no teratogenic effects.
Teratology:					
Rat	5 Female	PO	100, 200, 400, 600, 800	Days 6 to 15 of gestation	No teratogenicity. Maternal deaths at 600 and 800 mg/kg; decreased fetal body weights at ≥200 mg/kg.
Rat	20 Female	PO	UC[1], VC, 50, 150, 300	Days 6 to 15 of gestation	No fetotoxic or teratogenic effects. Reversible maternal toxicity.
Rabbit	5-7 Female	PO	10, 15, 25, 50, 100, 200, 400	Days 6 to 18 of gestation	Severe materno- and fetotoxicity.
Rabbit	5 Female	PO	VC, 1, 2, 4, 6, 8	Days 6 to 18 of gestation	Abortions and maternal deaths at 4, 6, and 8 mg/kg; materno- and fetotoxicity at doses >1 mg/kg.
Rabbit	14 Female	PO	VC 0.5, 1.0, 1.5	Days 6 to 18 of gestation	Not teratogenic. Maternal weight loss; increased incidence of postimplantation loss (embryotoxicity) at 1.0 and 1.5 mg/kg.
Perinatal/ Postnatal:					
Rat	20 Female	PO	VC, 25, 75, 150	Day 15 of gestation to Day 20 of lactation	Reduction in offspring body weights from birth to Day 21 postnatally at 25, 75, and 150 mg/kg.

[1] UC = Untreated Control; VC = Vehicle Control

Table 6: Genetic Toxicology Studies of Quinapril

Test		Dosage Range	Results
Mutagenicity			
1) *In Vitro* a)	Initial cytotoxicity in *Salmonella* strain	≤10,000 µg/plate	Non-cytotoxic.
b)	Mutagenesis assay in *Salmonella*	625-10,000 µg/plate	Negative-with or without metabolic activation.
2) *In Vitro* a)	Initial cytotoxicity assay	≤44,300 µg/mL	Cytotoxic at ≥1400 µg/mL.
b)	Point mutation assay in Chinese hamster lung cells	175-1400 µg/mL	Negative - did not manifest direct acting or promutagen activity.
Cytogenetics			
1) *In Vitro* a)	Initial cytotoxicity assay	≤44,300 µg/mL	Cytotoxic at concentrations >700 µg/mL.
b)	Sister chromatid exchange (SCE) assay in Chinese hamster ovary cells	10.94-1400 µg/mL	No increase in SCE at toxicity-limited doses ≤700 µg/mL in the presence of metabolic activation or ≤1400 µg/mL in the absence of metabolic activation.
2) *In Vitro* a)	Initial cytotoxicity assay	≤2700 µg/mL	Cytotoxic at ≥1200 µg/mL.
b)	Structural chromosomal aberration (SCA) assay in Chinese hamster lung cells	800-1800 µg/mL	Slight, statistically significant increase in SCA with metabolic activation; not considered biologically significant.
3) *In Vivo* a)	Mouse micronucleus assay	1-1430 µg/kg	Not clastogenic; no increased frequency of micronuclei.

Table 7: Carcinogenicity Studies of Quinapril

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Results
Mouse	104	50	PO	UC[1], VC[1], 5, 35, 75	No evidence of tumorigenic potential. Reduced heart weight, nephritis, and JGA hypertrophy/hyperplasia.
Rat	104	65	PO	UC, VC, 10, 50, 100	No evidence of tumorigenic potential. Reduced RBC, JGA hypertrophy/hyperplasia and renal degenerative changes.

[1] UC = Untreated Control; VC= Vehicle Control; JGA = juxtaglomerular apparatus; RBC = red blood cell count

Table 8: Toxicity Studies of Quinaprilat

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Results
A. Acute Studies:					
Mouse	Single-dose	10	IV	VC[1], 250, 500, 1000	No deaths; MLD >1000 mg/kg. No clinical or gross pathological changes.
Rat	Single-dose	10	IV	VC, 50, 100, 200, 300, 400	No deaths; MLD >400 mg/kg. No clinical or gross pathological changes.
Dog	Escalating doses	1	IV	Escalating; 1-240	No deaths; MLD >240 mg/kg. Reduced food consumption, weight loss, and slight increase in myeloid to erythroid ratio.
B. Subacute Studies:					
Rat	2	5	IV	VC, 25, 50, 100, 200	No deaths, clinical signs or adverse pathological findings.
Rat	4	10	IV	VC, 20, 100, 200	No drug-related deaths or clinical signs; reduced heart weights.
Dog	2	1	IV	VC, 10, 50, 100	Sporadic increases in heart rate.
Dog	4	3	IV	VC, 10, 50, 100	No clinical or gross pathologic findings; JGA hypertrophy/hyperplasia.

[1] VC = Vehicle Control; MLD = median lethol dose; JGA = juxtaglomerular apparatus

C. Genotoxicity Studies:

Test		Dosage Range	Results
Mutagenicity:			
In Vitro	a) Initial cytotoxicity in *Salmonella*	≤1200 µg/plate	Non-cytotoxic.
	b) Mutagenesis assay in *Salmonella*	75-1200 µg/plate	Negative-with or without metabolic activation.

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PART III: CONSUMER INFORMATION

ACCUPRIL®
(quinapril hydrochloride tablets)

Read this carefully before you start taking ACCUPRIL and each time you get a refill. This leaflet is a summary and will not tell you everything about ACCUPRIL. Talk to your doctor, nurse or pharmacist about your medical condition and treatment and ask if there is any new information about ACCUPRIL.

ABOUT THIS MEDICATION

What the medication is used for:

High Blood Pressure (Hypertension)

ACCUPRIL lowers high blood pressure. It can be used alone or together with a diuretic ("water pill").

Congestive Heart Failure

ACCUPRIL® is used for congestive heart failure (a condition where the heart is unable to pump enough blood for the body`s needs), when it is combined with either a diuretic ("water pill") and/or digitalis glycosides (drugs which help the heart beat more normally).

What it does:

ACCUPRIL is an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in '-PRIL'.

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking ACCUPRIL regularly even if you feel fine.

When it should not be used:

Do not take ACCUPRIL if you:

- Are allergic to quinapril hydrochloride or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures.
- Are taking Entresto (sacubitril/valsartan), due to the increased risk of serious allergic reaction which causes swelling of the face or throat (angioedema) when taken with ACCUPRIL.
- Are pregnant or intend to become pregnant. Taking ACCUPRIL during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. ACCUPRIL passes into breast milk.
- Have renovascular hypertension (a form of high blood pressure that affects the blood vessels leading to the kidney's).
- Are taking aliskiren-containing medicines, such as Rasilez, **and** have one of the following conditions:
  - Diabetes
  - Kidney disease
  - High levels of potassium
  - Congestive heart failure combined with hypotension.
- Are taking an angiotensin receptor blocker (ARB), another medicine to treat your high blood pressure, or another ACE inhibitor **and** have one of the following conditions:
  - Diabetes with end organ damage
  - Kidney disease
  - High levels of potassium
  - Congestive heart failure combined with hypotension.

You can recognize ARBs because their medicinal ingredient ends in "-**SARTAN**".

- Have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

Because lactose is a non-medicinal ingredient in ACCUPRIL.

What the medicinal ingredient is:

Quinapril hydrochloride

What the nonmedicinal ingredients are:

Candelilla wax, crospovidone, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, magnesium carbonate, magnesium stearate, polyethylene glycol, synthetic red iron oxide, titanium dioxide.

What dosage forms it comes in:

Tablets; 5, 10, 20, 40 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy
ACCUPRIL® should not be used during pregnancy. If you discover that you are pregnant while taking ACCUPRIL®, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use ACCUPRIL talk to your doctor, nurse, or pharmacist if you:

- Are allergic to any drug used to lower blood pressure.
- Have recently received or are planning to get allergy shots for bee or wasp stings.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Are on dialysis or receiving LDL apheresis (treatment to remove "bad cholesterol" from the blood).
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.

- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Are taking an antibiotic containing trimethoprim.
- Are on a low-salt diet.
- Are receiving gold (sodium aurothiomalate) injections.
- Are less than 18 years old.
- Are taking a neutral endopeptidase inhibitor. The combination with ACCUPRIL is not recommended.
- Are taking a medicine that contains aliskiren, such as Rasilez, an angiotensin receptor blocker (ARB) or another ACE inhibitor (in addition to ACCUPRIL). The combination with ACCUPRIL is not recommended.
- Are taking anti-cancer (temsirolimus, everolimus), anti-rejection (sirolimus) or anti-diabetic (gliptins) drugs. Use of ACE inhibitors, such as ACCUPRIL, with these drugs may increase the chance of having an allergic reaction.

You may become sensitive to the sun while taking ACCUPRIL. Exposure to sunlight should be minimized until you know how you respond.

If you are going to have surgery and will be given an anesthetic, be sure to tell your doctor or dentist that you are taking ACCUPRIL.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to ACCUPRIL. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with ACCUPRIL:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, a potassium-sparing diuretic (a specific kind of "water pill") or sulfamethoxazole/trimethoprim.
- Alcohol
- Allopurinol used to treat gout.
- Anti-cancer drugs, including cyclophosphamide, methotrexate and temsirolimus and everolimus
- Anti-rejection drugs, such as sirolimus (Rapamune)
- Anti-diabetic drugs including insulin and oral medicines (e.g. metformin, gliptins, sulfonylureas)
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), angiotensin receptor blockers (ARBs) or other ACE inhibitors (in addition to ACCUPRIL).
- Gold for the treatment of rheumatoid arthritis.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Tetracycline (a type of antibiotic)

PROPER USE OF THIS MEDICATION

Take ACCUPRIL exactly as prescribed. It is recommended to take your dose at about the same time every day.

Usual Adult Dose:

High Blood Pressure (Hypertension)
For patients not taking a diuretic ("water pills"): The recommended starting dose is 10 mg once a day.

For patients also taking a diuretic ("water pill"): The recommended starting dose is 5 mg once a day.

Congestive Heart Failure
The recommended starting dose is 5 mg once a day.

Overdose:

If you think you have taken too much ACCUPRIL contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Dizziness, headache, trouble sleeping
- drowsiness, fatigue, weakness
- cough, stuffy and runny nose
- rash, itching
- abdominal pain, diarrhea, indigestion, nausea, vomiting
- back pain

If any of these affects you severely, tell your doctor, nurse or pharmacist.

ACCUPRIL can cause abnormal blood test results. Your doctor

will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Low blood pressure:** dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	√		
	Increased levels of potassium in the blood: irregular heartbeat, muscle weakness and generally feeling unwell		√	
Uncommon	**Allergic reaction, including angioedema:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Kidney disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Liver disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Electrolyte imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
	Tachycardia: Fast heart beat		√	
	Edema: Swelling of hands, ankles or feet		√	
Rare	**Decreased platelets:** bruising, bleeding, fatigue and weakness		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Decreased white blood cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
	Chest Pain , heart attack			√
	Shortness of breath	√		
	Coughing up blood			√
	High nitrogen compound found in blood (Azotemia): rapid heart rate, high blood pressure, fatigue, confusion, light headedness, dizziness, decreased urine production			√

This is not a complete list of side effects. For any unexpected effects while taking ACCUPRIL, contact your doctor, nurse, or pharmacist.

HOW TO STORE IT

Store ACCUPRIL® at room temperature, between 15° and 30° C. Protect from moisture. Keep in well closed container.

Keep ACCUPRIL® out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca.or by contacting the sponsor, Pfizer Canada Inc., at:

1-800-463-6001

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