Accupril®

اکوپرل® ٹیبلیٹس

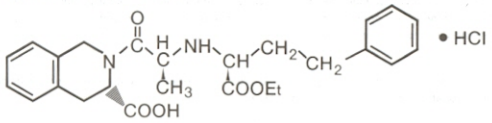
Quinapril hydrochloride Tablets – 5, 10 and 20 mg

PI001R1

DESCRIPTION

Quinapril hydrochloride is the salt of quinapril, the ethyl ester of a nonsulfhydryl, angiotensinconverting enzyme (ACE) inhibitor, quinaprilat.

Quinapril hydrochloride is chemically described as [3S-[2[R*(R*)], 3R*]]-2-[2-[[1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-l-oxopropyl]- 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. Its empirical formula is $C_{25}H_{30}N_2O_5$ • HCl and its structural formula is



M.W.=474.98

Quinapril hydrochloride is a white to off-white amorphous powder, freely soluble in aqueous solvents with a melting point of 108° to 115°C.

Quinapril is supplied as 5 mg, 10 mg, and 20 mg tablets for oral administration. Inactive ingredients include magnesium carbonate, magnesium stearate, lactose, and gelatin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Quinapril is rapidly deesterified to quinaprilat (quinapril diacid, the principal metabolite) which, in human and animal studies, is a potent angiotensin-converting enzyme inhibitor. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II which is involved in vascular control and function through many different mechanisms, including stimulation of aldosterone secretion by the adrenal cortex. The mode of action of quinapril in humans and animals is to inhibit circulating and tissue ACE activity, thereby decreasing vasopressor activity and aldosterone secretion. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. Quinapril monotherapy was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in nonblacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.[1,2]

In animal studies, the antihypertensive effect of quinapril outlasts its inhibitory effect on circulating ACE, whereas, tissue ACE inhibition more closely correlates with the duration of its antihypertensive effects.[3,4]

ACE inhibitors, including quinapril, may enhance insulin sensitivity.[5]

Pharmacokinetics and Metabolism

Following oral administration, peak plasma quinapril concentrations are observed within one hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is approximately 60%. Thirty-eight percent of orally administered quinapril is systemically available as quinaprilat, Quinapril has an apparent half-life in plasma of approximately one hour. Peak plasma quinaprilat concentrations are observed approximately two hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of approximately three hours. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins. In patients with renal insufficiency, the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. 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.[6,7] There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. The elimination of quinaprilat is also reduced in elderly patients (≥65 years) and correlates well with their level of renal function. (See DOSAGE AND ADMINISTRATION.) Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

Pharmacodynamics

Administration of 10 to 40 mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. Antihypertensive activity commences within one hour[8] with peak effects usually achieved by two to four hours after dosing.[9,10,11] Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24-hour dosing interval[12,13] and continue during long-term therapy.[14,15]

Hemodynamic assessments in patients with hypertension have indicated that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate or filtration fraction.[16]

Concomitant therapy with thiazide-type diuretics and/or the addition of beta-blocker therapy enhances the antihypertensive effects of quinapril, giving a blood pressure lowering effect greater than that seen with either agent alone.

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 the incidence of adverse events in elderly patients.[17]

Quinapril administration to patients with congestive heart failure reduces peripheral vascular resistance, mean arterial pressure, systolic and diastolic blood pressure, pulmonary capillary wedge pressure, and increases cardiac output.

In 149 patients undergoing elective coronary bypass surgery, treatment with quinapril 40mg reduced the incidence of post-operative ischemic events compared to placebo during a one year follow-up.[18]

In patients with documented coronary artery disease but without manifest hypertension or heart failure, quinapril improves abnormal endothelial function measured in coronary[19] and brachial arteries.[20]

Quinapril enhances endothelial function by mechanisms leading to increased availability of nitric oxide. Endothelial dysfunction is considered an important underlying pathophysiological mechanism in CAD. The clinical significance of improving endothelial function has not been established.

INDICATIONS AND USAGE

Hypertension

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

Congestive Heart Failure

Quinapril is effective in the treatment of congestive heart failure when given concomitantly with a diuretic and/or cardiac glycoside.

CONTRAINDICATIONS

Quinapril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Cross-sensitivity to other ACE inhibitors has not been evaluated.

WARNINGS

Angioedema: Angioedema has been reported in patients treated with angiotensin-converting enzyme inhibitors, including in 0.1% of patients receiving quinapril. If laryngeal stridor or angioedema of the face, tongue, or glottis occur, treatment with quinapril should be discontinued immediately; the patient should be 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; antihistamines may be useful in relieving symptoms. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate emergency therapy, including, but not limited to subcutaneous adrenalin (epinephrine) solution 1: 1000 (0.3 to 0.5 mL), should be promptly administered. (See ADVERSE REACTIONS.)

Black patients receiving ACE inhibitor therapy have been reported to have a higher incidence of angioedema compared to non-black patients. It should also be noted that in controlled clinical trials, ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. The incidence of angioedema in black and non-black patients during quinapril therapy has been calculated in two large open label clinical trials evaluating the effectiveness of quinapril in the management of hypertension. In one study wherein 1656 black and 10583 non-black patients were evaluated, the incidence of angioedema, regardless of association to quinapril treatment was 0.3% in blacks, and 0.39% in non-blacks. In the other study, (1443 black and 9300 non-black patients) the incidence of angioedema was 0.55% in blacks, and 0.17% in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Anaphylactoid reactions

Desensitization: Patients receiving ACE inhibitors during desensitizing treatment with hymenoptera venom have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they have reappeared upon inadvertent rechallenge.[21]

LDL apheresis: Patients undergoing low-density lipoprotein apheresis with dextran-sulfate absorption when treated concomitantly with an ACE inhibitor, have reported anaphylactoid reactions.[22,23]

Hemodialysis: Clinical evidence has shown that patients hemodialysed using certain high-flux membranes (such as polyacrylonitrile membranes) are likely to experience anaphylactoid reactions with concomitant ACE inhibitor treatment. This combination should be avoided, either by use of alternative antihypertensive drugs, or alternative membranes for hemodialysis.[24]

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with quinapril but is a possible consequence of ACE inhibition therapy in salt/volume depleted patients such as those previously treated with diuretics, who have a dietary salt restriction, or who are on dialysis. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS.)

In patients with congestive heart failure, who are at risk of excessive hypotension, quinapril therapy should be started at the recommended dose under close medical supervision; these patients should be followed closely for the first two weeks of treatment and whenever the dosage of quinapril is increased.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses; however, lower doses of quinapril or any concomitant diuretic therapy should be considered if this event occurs.

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

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

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Before quinapril is used during pregnancy, the possible adverse effects on the fetus must be considered. Should a woman become pregnant while receiving quinapril, the drug should be discontinued.

When ACE, inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the fetus; limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios.[25,26,27] While these adverse effects do not appear to have been the result of exposure limited to the first trimester, mothers whose embryos and fetuses have been exposed only during the first trimester, must be so informed. Nonetheless, should a woman become pregnant while receiving ACE inhibitors, the drug should be discontinued as soon as possible.

Patients who do require ACE inhibitors during the second and third trimesters of pregnancy should be apprised of the potential hazards to the fetus; frequent ultrasound examinations should be performed to detect oligohydramnios. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, quinapril should be discontinued unless it is considered life-saving for the mother.

Other potential risks to the fetus/neonate exposed to ACE inhibitors include intrauterine growth retardation, prematurity, and patent ductus arteriosus; fetal death also has been reported. It is not clear, however, whether these reported events are related to ACE inhibition or the underlying maternal disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Infants exposed *in utero* 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.

PRECAUTIONS

General

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

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

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when quinaprill has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment Dosage reduction and/or discontinuation of a diuretic and/or quinapril may be required.[28]

ACE inhibitors have been associated with hypoglycemia in diabetic patients on insulin or oral hypoglycemic agents; closer monitoring of diabetic patients may be required.[29]

Hyperkalemia and potassium-sparing diuretics: As with other ACE inhibitors, patients on quinapril alone may have increased serum potassium levels. When administered concomitantly, quinapril may reduce the hypokalemia induced by thiazide diuretics. Quinapril has not been studied as concomitant therapy with potassium-sparing diuretics. Because of the risk of further potentiating increases in serum potassium it is advised that combination therapy with potassium-sparing diuretics be initiated with caution and the patient's serum potassium levels be closely monitored. (See PRECAUTIONS and Drug Interactions.)

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

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors. These patients should be asked to report pregnancies to their physicians immediately.

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of quinapril. Patients should be advised that if any sign or symptom suggesting angioedema occurs (i.e., swelling of face, extremities, eyes, lips, tongue; difficulty in swallowing or breathing), they should immediately stop taking quinapril and consult with their physician. (See WARNINGS.)

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of quinapril therapy. If syncope occurs, the patients should be told not to take the drug until they have consulted with their physician. (See WARNINGS.)

All patients should be cautioned that inadequate fluid intake, excessive perspiration, or dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician. (See PRECAUTIONS.)

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), as this could be a sign of neutropenia.

Patients planning to undergo surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

NOTE: As with many other drugs, certain advice to patients being treated with quinapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Tetracycline: Administration of tetracycline with quinapril reduced the absorption of tetracycline by approximately 28% to 37% in subjects. Decreased absorption is due to the presence of magnesium carbonate as an excipient in the quinapril formulation. This interaction should be considered if coprescribing quinapril and tetracycline.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy due to the sodium-losing effect of these agents. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity[30]

Other Agents: No clinically important pharmacokinetic interactions occurred when quinapril was used concomitantly with propranolol, hydrochlorothiazide, digoxin or cimetidine. The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice daily.[31]

Concomitant Diuretic Therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with quinapril. Hypotensive effects after the first dose of quinapril may be minimized by discontinuing the diuretic a few days prior to intiation of therapy. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced. In patients in whom a diuretic is continued, medical supervision should be provided for up to two hours after the initial dosage of quinapril. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Increasing Serum Potassium: If concomitant therapy of quinapril with potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution and with appropriate monitoring of serum potassium.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively) for 104 weeks. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister-chromatid exchange in cultured mammalian cells, micronucleus test with mice. *in vitro* chromosome aberration with V79 cultured lung cells, and an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at dose levels up to 100 mg/kg/day (60 times the maximum daily human dose).

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 times 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 or more. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at doses as low as 0.5 mg/kg/day and 1 mg/kg/day, respectively.

Pregnancy

See WARNNGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

ACE inhibitors, including quinapril, are secreted in human milk to a limited extent.[32,33,34] Because of this, caution should be exercised when quinapril is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased AUC and peak levels for quinaprilat compared to values in younger patients; this appeared to be related to decreased renal function rather than age itself. In controlled and uncontrolled studies where 21% of patients were 65 years or older, no overall differences, in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

Safety and effectiveness of quinapril in pediatric patients have not been established.

ADVERSE REACTIONS

Quinapril has been evaluated for safety in 4960 subjects and patients and was well tolerated. Of these, 3203 patients including 655 elderly patients, participated in controlled clinical trials. Quinaprill has been evaluated for long-term safety in over 1400 patients treated for one year or more.[17]

Adverse experiences were usually mild and transient in nature. The most frequent clinical adverse reactions in controlled trials were headache (7.2%), dizziness (5.5%), cough (3.9%), fatigue (3.5%), rhinitis (3.2%), nausea and/or vomiting (2.8%), and myalgia (2.2%). It should be noted that characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Discontinuation of therapy because of adverse events was required in 5.2% of the patients treated with quinapril in controlled clinical trials.

Adverse experiences occurring in 1% or more of the 3203 patients in controlled clinical trials who were treated with quinapril with or without a concomitant diuretic are shown below. Incidence of adverse experiences in the subset of 655 patients 65 years and older is given for comparison. A subset of the 2005 patients in controlled clinical trials who were treated with quinapril monotherapy for hypertension is also presented.

Percent of Patients in Controlled Studies

	Quinapril ± Diuretic		Monotherapy	
	%			Placebo
Adverse Event	Total N = 3203*	≥ 65 yrs N = 655	% N = 2005**	% N = 579**
Headache	7.2	4.0	8.1	16.9
Dizziness	5.5	6.6	4.1	4.3
Coughing	3.9	4.1	3.2	1.4
Fatigue	3.5	3.5	3.2	2.1
Rhinitis	3.2	2.1	3.2	4.5
Nausea a/o vomiting	2.8	3.8	2.3	2.6
Myalgia	2.2	1.2	1.7	3.3
Diarrhea	2.0	2.4	1.9	1.0
Chest Pain	2.0	1.8	1.2	1.9
Upper Respiratory Infection	2.0	0.6	2.3	2.2
Abdominal Pain	1.9	1.8	2.0	2.2
Viral Infection	1.8	0.6	2.0	2.4
Dyspepsia	1.6	1.2	1.9	1.2
Dyspnea	1.5	2.3	0.9	0.5
Back Pain	1.4	1.7	1.3	1.0
Asthenia	1.3	1.4	1.0	1.0
Pharyngitis	1.3	0.5	1.5	1.9
Insomnia	1.3	0.8	1.3	0.7
Hypotension	1.1	1.8	1.0	0.0
Sinusitis	1.1	0.3	1.2	2.4
Paresthesia	1.1	0.9	1.0	0.9
Bronchitis	1.0	0.8	0.9	1.2

* Includes 454 patients treated for congestive heart failure

** Includes patients treated for hypertension only

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

Cardiovascular :	palpitations, vasodilation, angina pectoris, tachycardia
Gastrointestinal :	flatulence, dry mouth or throat, pancreatitis
Nervous/Psychiatric :	vertigo, nervousness, depression, somnolence
Integumentary :	pruritus, increased perspiration, rash, alopecia, pemphigus, exfoliative dermatitis
Urogenital :	urinary tract infection impotence
Other :	edema, arthralgia, amblyopia, hemolytic anemia
Rare Events :	Angioedema was reported in patients receiving quinapril (0.1%). (See WARNINGS and CONTRAINDICATIONS.) While rarely seen with quinapril, eosinophilic pneumonitis, hepatitis or hepatic failure have been reported with other ACE inhibitors.

Clinical Laboratory Test Findings

Agranulocytosis and neutropenia have been rarely reported and the causal relationship to quinapril is unclear. (See WARNINGS.)

Hyperkalemia: (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 quinapril alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on quinapril alone. These increases often reversed on continued therapy.

OVERDOSAGE

The oral LD_{50} of quinapril in mice and rats ranges from 1440 to 4280 mg/kg.
No specific information is available on the treatment of overdosage with quirapril. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion. Treatment is symptomatic and supportive consistent with established medical care.

Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.[6,7]

DOSAGE AND ADMINISTRATION

Hypertension

Monotherapy: The recommended initial dosage of quinapril in patients not on diuretics is 10 or 20 mg once daily. Depending upon clinical response, the patient's dosage may be titrated (by doubling the dose) to a maintenance dosage of 20 or 40 mg/day usually given as a single dose or may be divided in 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 quinapril up to 80 mg per day.

Concomitant Diuretics: In patients who must continue treatment with a diuretic, the initial recommended dosage of quinapril is 5 mg which should subsequently be titrated (as described above) to the optimal response. (See Drug Interactions.)

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.[35,36]

Creatinine Clearance (mL/min)	Maximum Recommended Initial Dosage (mg)
>60	10
30-60	5
10-30	2.5
<10	*

* There is insufficient experience at this time, to allow for specific dosage recommendations in these patients.

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

Quinapril is indicated as adjunctive therapy with diuretics and/or cardiac glycosides. The recommended initial dosage in patients with congestive heart failure is 5 mg once or twice daily, following which the patient should be monitored closely for symptomatic hypotension. If the initial dose of quinapril is well tolerated, patients may be titrated up to an effective dose, usually l0 to 40 mg per day given in two equally divided doses with concomitant therapy.[37,38,39]

Renal Impairment: Kinetic data indicate that quinapril elimination is dependent on the level of renal function. The recommended initial dose of quinapril is 5 mg in patients with a creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance less than 30 mL/min. If the initial dose is well tolerated, quinapril may be administered the following day as a twice daily regimen. In the absence of excessive hypotension or significant deterioration of renal function, the dose may be increased at weekly intervals based of clinical and hemodynamic response.

HOW SUPPLIED

Accupril 5mg tablets is available in strips of 2 x 14's
Accupril l0mg tablets is available in strips of 2 x 14's
Accupril 20mg tablets is available in strips of 2 x 14's

STORAGE

Store at room temperature 25°C (77°F) and in a dry place.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

Marketed by :
Parke, Davis & Co., Ltd.
B-2, S.I.T.E., Karachi-Pakistan.

PARKE-DAVIS

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Mooswaldallee 1
D-79090 Freiburg, Germany.

443 142