EXHIBIT C

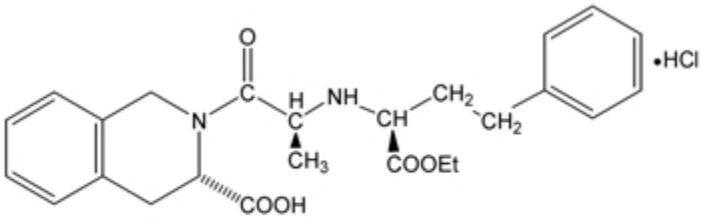
QUINAPRIL HYDROCHLORIDE - quinapril hydrochloride tablet, film coated
Mylan Pharmaceuticals Inc.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, quinapril should be discontinued as soon as possible. See WARNINGS: Fetal/ Neonatal Morbidity and Mortality.

DESCRIPTION

Quinapril hydrochloride is the hydrochloride salt of quinapril, the ethyl ester of a nonsulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat.
Quinapril hydrochloride is chemically described as [3S-[2[R*(R*)], 3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4- tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. Its molecular formula is $C_{25}H_{30}N_2O_5$ • HCl and its structural formula is:



M.W.=474.98

Quinapril hydrochloride, USP is a white to off-white amorphous powder that is freely soluble in aqueous solvents.
Quinapril tablets, USP contain 5 mg, 10 mg, 20 mg, or 40 mg of quinapril for oral administration. Each tablet also contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, FD&C Yellow No. 6 aluminum lake, hypromellose, magnesium carbonate, magnesium stearate, microcrystalline cellulose, povidone, polydextrose, polyethylene glycol, sodium lauryl sulfate and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, norepinephrine or epinephrine. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with quinapril alone resulted in mean increases in potassium of 0.07 mmol/L (see PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased 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 was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in non-blacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

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 at least 60%. The rate and extent of quinapril absorption are diminished moderately (approximately 25 to 30%) when quinapril tablets are administered during a high fat meal. Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of quinapril, there is an effective accumulation half-life of quinaprilat of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose. Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose, and has an elimination half-life in plasma of approximately 2 hours and a prolonged terminal phase with a half-life of 25 hours. The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5 mg to 80 mg doses and 40 mg to 160 mg in multiple daily doses. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic hemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. 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 deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

Pharmacodynamics and Clinical Effects

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

Administration of 10 mg to 80 mg of quinapril to patients with mild to severe hypertension results in a reduction of sitting and standing blood pressure to about the same extent with minimal effect on heart rate. Symptomatic postural hypotension is infrequent although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS). Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2 to 4 hours after dosing. During chronic therapy, most of the blood pressure lowering effect of a given dose is obtained in 1 to 2 weeks. In multiple-dose studies, 10 mg to 80 mg per day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5 to 11/3 to 7 mm Hg. The trough effect represents about 50% of the peak effect. While the dose-response relationship is relatively flat, doses of 40 mg to 80 mg were somewhat more effective at trough than 10 mg to 20 mg, and twice daily dosing tended to give a somewhat lower trough blood pressure than once daily dosing with the same total dose. The antihypertensive effect of quinapril continues during long-term therapy, with no evidence of loss of effectiveness.

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

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

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

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 adverse events in elderly patients.

INDICATIONS AND USAGE

Hypertension
Quinapril tablets are indicated for the treatment of hypertension. They may be used alone or in combination with thiazide diuretics. In using quinapril tablets, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that quinapril tablets do not have a similar risk (see WARNINGS).

Angioedema in Black Patients
Black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. It should also be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

CONTRAINDICATIONS
Quinapril tablets are 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.

WARNINGS

Anaphylactoid and Possibly Related Reactions
Presumably because angiotensin-converting inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including quinapril) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema
Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving quinapril.

In two similarly sized U.S. post-marketing trials that, combined, enrolled over 3,000 black patients and over 19,000 non-blacks, angioedema was reported in 0.30% and 0.55% of blacks (in study 1 and 2 respectively) and 0.39% and 0.17% of non-blacks.

Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with quinapril should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

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.

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

Anaphylactoid Reactions During Desensitization
Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hepatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hypotension
Excessive hypotension is rare in patients with uncomplicated hypertension treated with quinapril alone. Patients with heart failure given quinapril commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. Caution should be observed when initiating therapy in patients with heart failure. In controlled studies, syncope was observed in 0.4% of patients (N = 3,203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include patients with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or cautiously increase salt intake (except in patients with heart failure) before initiating therapy with quinapril in patients at risk for excessive hypotension who are able to tolerate such adjustments.

In patients at risk of excessive hypotension, therapy with quinapril should be started under close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of quinapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If excessive 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 of quinapril, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of quinapril or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis
Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during quinapril treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of quinapril are insufficient to show that, in patients without prior reactions to other ACE inhibitors, quinapril does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic 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 death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors 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, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of quinapril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, quinapril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories 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 disordered renal function. Removal of quinapril, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of quinapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

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.

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

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

Evaluation of patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and Potassium-Sparing Diuretics
In clinical trials, hyperkalemia (serum potassium ≥ 5.8 mmol/L) occurred in approximately 2% of patients receiving quinapril. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with quinapril (see PRECAUTIONS: Drug Interactions).

Cough
Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, quinapril 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.

Information for Patients

Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema
Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic Hypotension
Patients should be cautioned that lightheadedness can occur, especially during the first few days of quinapril therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

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

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) which could be a sign of neutropenia.

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

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. The possibility of hypotensive effects with quinapril may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with quinapril. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium
Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. 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 along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and Other Drugs That Interact with Magnesium
Simultaneous administration of tetracycline with quinapril reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in quinapril tablets. This interaction should be considered if coprescribing quinapril and tetracycline or other drugs that interact with magnesium.

Lithium
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. 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.

Gold
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.

Other Agents
Drug interaction studies of quinapril with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of quinapril.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice daily.
- Quinapril treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of quinapril and hydrochlorothiazide were administered concomitantly.
- Coadministration of multiple 10 mg doses of atorvastatin with 80 mg of quinapril resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

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, on an mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on an mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. 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 in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers
Because quinapril is secreted in human milk, caution should be exercised when this drug is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of quinapril in pediatric patients have not been established.

Geriatric Use
Clinical studies of quinapril did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
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.
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.

ADVERSE REACTIONS

Hypertension
Quinapril has been evaluated for safety in 4,960 subjects and patients. Of these, 3,203 patients, including 655 elderly patients, participated in controlled clinical trials. Quinapril has been evaluated for long-term safety in over 1,400 patients treated for 1 year or more.
Adverse experiences were usually mild and transient.
In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 4.7% of patients with hypertension.
Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1,563 patients in placebo-controlled hypertension trials who were treated with quinapril are shown below.
Adverse Events in Placebo-Controlled Trials

	Quinapril (N = 1,563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1
Coughing	2 (0.5)	0
Nausea and/or Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1 (0.2)	0.7

Clinical adverse experiences probably, possibly, or definitely related, or of uncertain relationship to therapy occurring in 0.5% to 1% (except as noted) of the patients with hypertension treated with quinapril (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4,847) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):
General: back pain, malaise, viral infections, *anaphylactoid reaction*
Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances, cardiogenic shock*
Hematology:*hemolytic anemia*
Gastrointestinal: flatulence, dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests, dyspepsia*
Nervous/Psychiatric: somnolence, vertigo, syncope, nervousness, depression, insomnia, paresthesia
Integumentary: alopecia, increased sweating, pemphigus, pruritus, *exfoliative dermatitis, photosensitivity reaction, dermatopolymyositis*
Urogenital: urinary tract infection, impotence, *acute renal failure, worsening renal failure*
Respiratory:*eosinophilic pneumonitis*
Other: amblyopia, edema, arthralgia, pharyngitis, *agranulocytosis, hepatitis, thrombocytopenia*

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Angioedema
Angioedema has been reported in patients receiving quinapril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with quinapril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology
(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 all 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 remit on continued therapy.

OVERDOSAGE
Doses of 1440 to 4280 mg/kg of quinapril cause significant lethality in mice and rats.
No specific information is available on the treatment of overdosage with quinapril. The most likely clinical manifestation would be symptoms attributable to severe hypotension.
Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose.
No data are available to suggest physiological maneuvers (e.g., maneuvers to change pH of the urine) that might accelerate elimination of quinapril and its metabolites.
Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of quinapril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of quinapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat quinapril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Hypertension

Monotherapy
The recommended initial dose of quinapril tablets in patients not on diuretics is 10 mg or 20 mg once daily. Dosage should be adjusted according to blood pressure response measured at peak (2 to 6 hours after dosing) and trough (predosing). Generally, dosage adjustments should be made at intervals of at least 2 weeks. Most patients have required dosages of 20, 40, or 80 mg/day, given as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice daily administration may be warranted. In general, doses of 40 mg to 80 mg and divided doses give a somewhat greater effect at the end of the dosing interval.

Concomitant Diuretics
If blood pressure is not adequately controlled with quinapril monotherapy, a diuretic may be added. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of quinapril tablets. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2 to 3 days prior to beginning therapy with quinapril tablets (see WARNINGS). Then, if blood pressure is not controlled with quinapril tablets alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg quinapril tablets should be used with careful medical supervision for several hours and until blood pressure has stabilized.

The dosage should subsequently be titrated (as described above) to the optimal response (see WARNINGS, PRECAUTIONS: Drug Interactions).

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

Creatinine Clearance	Maximum Recommended Initial Dose

> 60 mL/min	10 mg
30 to 60 mL/min	5 mg
10 to 30 mL/min	2.5 mg
< 10 mL/min	Insufficient data for dosage recommendation

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

Elderly (≥ 65 years)
The recommended initial dosage of quinapril tablets in elderly patients is 10 mg given once daily followed by titration (as described above) to the optimal response.

Following the initial dose of quinapril tablets, the patient should be observed under medical supervision for at least two hours for the presence of hypotension or orthostasis and, if present, until blood pressure stabilizes. The appearance of hypotension, orthostasis, or azotemia early in dose titration should not preclude further careful dose titration. Consideration should be given to reducing the dose of concomitant diuretics.

Dose Adjustments in Patients with Heart Failure and Renal Impairment or Hyponatremia
Pharmacokinetic data indicate that quinapril elimination is dependent on level of renal function. In patients with heart failure and renal impairment, the recommended initial dose of quinapril is 5 mg in patients with a creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance of 10 to 30 mL/min. There is insufficient data for dosage recommendation in patients with a creatinine clearance less than 10 mL/min. (See WARNINGS and PRECAUTIONS: Drug Interactions.)
If the initial dose is well tolerated, quinapril tablets 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 on clinical and hemodynamic response.

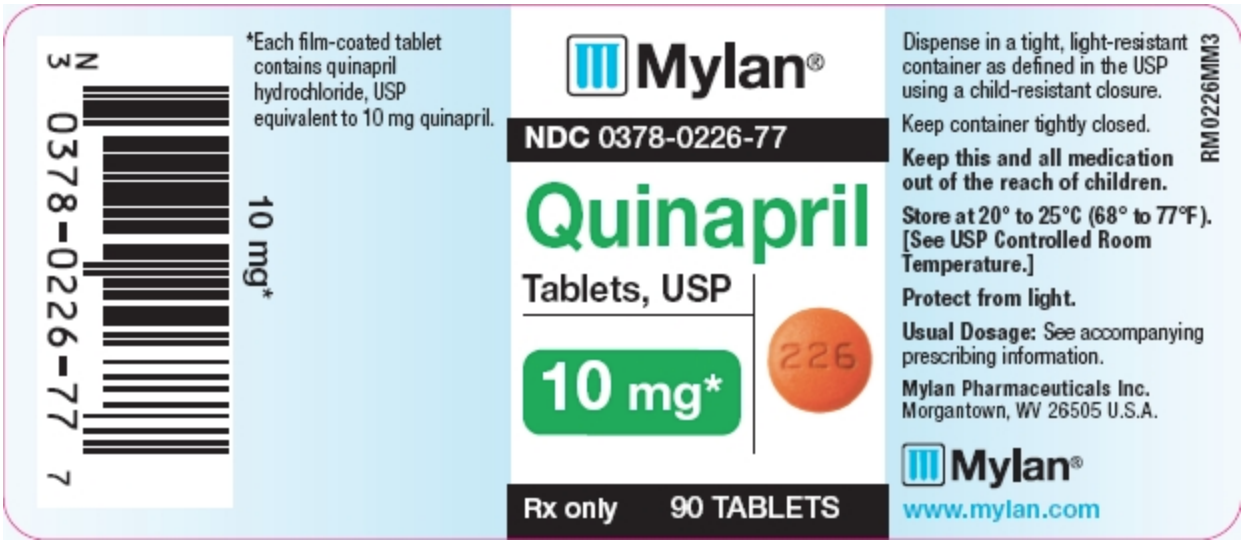
HOW SUPPLIED
Quinapril Tablets, USP are available containing 5 mg, 10 mg, 20 mg or 40 mg of quinapril, USP.
The 5 mg tablets are orange film-coated, round, scored tablets debossed with **M** on one side of the tablet and **1** to the left of the score and **7** to the right of the score on the other side. They are available as follows:
NDC 0378-1117-77
bottles of 90 tablets
NDC 0378-1117-05
bottles of 500 tablets
The 10 mg tablets are orange film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **226** on the other side. They are available as follows:
NDC 0378-0226-77
bottles of 90 tablets
NDC 0378-0226-05
bottles of 500 tablets
The 20 mg tablets are orange film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **254** on the other side. They are available as follows:
NDC 0378-0254-77
bottles of 90 tablets
NDC 0378-0254-05
bottles of 500 tablets
The 40 mg tablets are orange film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **272** on the other side. They are available as follows:
NDC 0378-0272-77
bottles of 90 tablets
Store at 20° to 25 °C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
REVISED DECEMBER 2010
QNPL:R6
PRINCIPAL DISPLAY PANEL - 5 mg
NDC 0378-1117-77

Quinapril
Tablets, USP
5 mg*
Rx only 90 TABLETS
*Each film-coated tablet
contains quinapril
hydrochloride, USP
equivalent to 5 mg quinapril.
Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication
out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from light.
Usual Dosage: See accompanying
prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
www.mylan.com
RM1117MM1

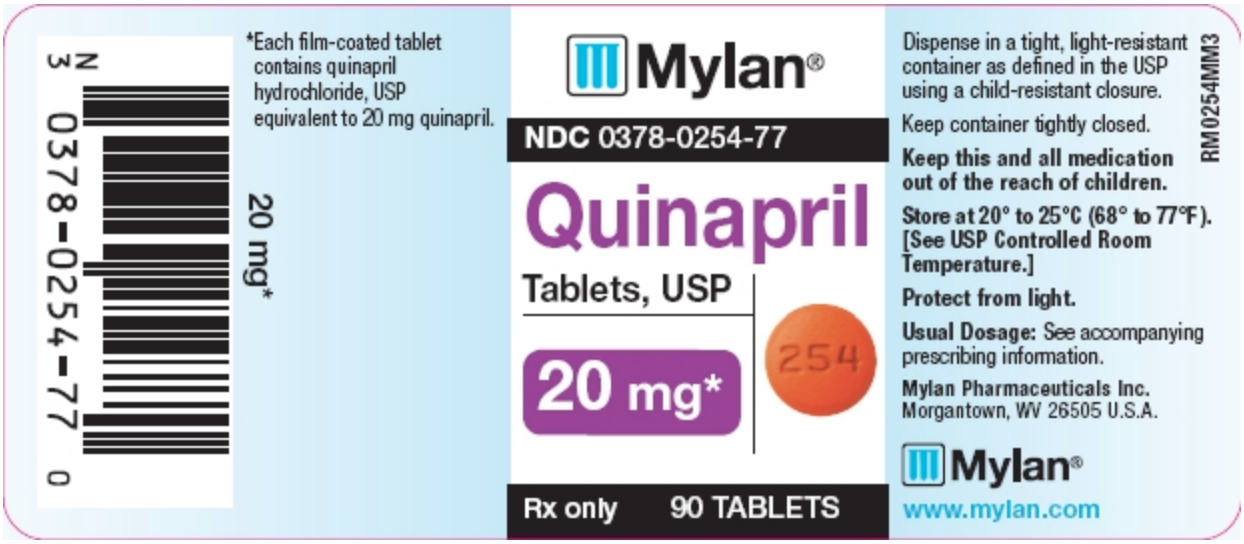


PRINCIPAL DISPLAY PANEL - 10 mg
NDC 0378-0226-77
Quinapril
Tablets, USP
10 mg*
Rx only 90 TABLETS
*Each film-coated tablet
contains quinapril
hydrochloride, USP
equivalent to 10 mg quinapril.
Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication
out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room

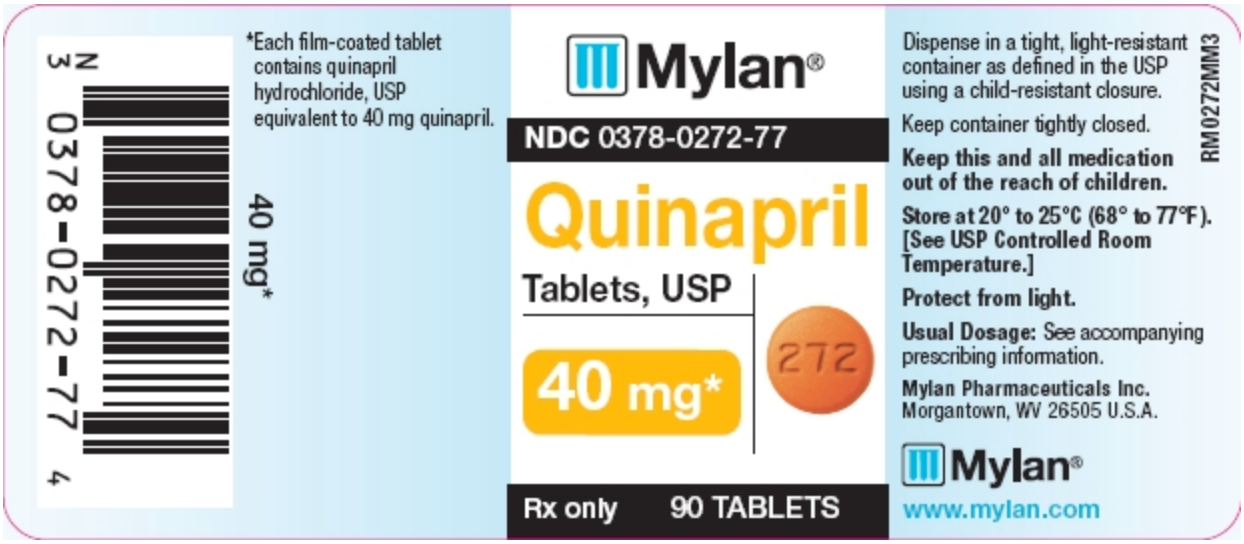
Temperature.]
Protect from light.
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
www.mylan.com
RM0226MM3



PRINCIPAL DISPLAY PANEL - 20 mg
NDC 0378-0254-77
Quinapril
Tablets, USP
20 mg*
Rx only 90 TABLETS
*Each film-coated tablet contains quinapril hydrochloride, USP equivalent to 20 mg quinapril.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light.
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
www.mylan.com
RM0254MM3



PRINCIPAL DISPLAY PANEL - 40 mg
NDC 0378-0272-77
Quinapril
Tablets, USP
40 mg*
Rx only 90 TABLETS
*Each film-coated tablet
contains quinapril
hydrochloride, USP
equivalent to 40 mg quinapril.
Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication
out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from light.
Usual Dosage: See accompanying
prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
www.mylan.com
RM0272MM3


N 3 0378-0272-77 4
*Each film-coated tablet contains quinapril hydrochloride, USP equivalent to 40 mg quinapril.
40 mg*
Mylan®
NDC 0378-0272-77
Quinapril
Tablets, USP
40 mg*
272
Rx only
90 TABLETS
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light.
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan®
www.mylan.com
RM0272MM3