

NEW ZEALAND DATA SHEET

1. NAME OF THE MEDICINE

Arrow – Quinapril 5, film-coated tablets, 5 mg
Arrow – Quinapril 10, film-coated tablets, 10 mg
Arrow – Quinapril 20, film-coated tablets, 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg, 10 mg or 20 mg of quinapril as quinapril hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets 5 mg: Yellow, oval, biconvex film coated tablets, one side scored and embossed '5' on the other side.

Tablets 10 mg: White to almost white, round, biconvex film coated tablets, one side scored and embossed '10' on the other side.

Tablets 20 mg: Yellow, round, biconvex film coated tablets, one side scored and embossed '20' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Quinapril is indicated for the treatment of essential hypertension. Quinapril is effective as monotherapy or concomitantly with 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 digoxin.

4.2 Dose and method of administration

Hypertension in Adults

Monotherapy

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

Concomitant Diuretics

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

Renal Impairment

Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases.

Recommended starting dosages based on clinical and pharmacokinetic data from patients with renal impairment are as follows:

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

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

Congestive Heart Failure in Adults

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

Paediatric Population

Not recommended for children.

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

Pharmacokinetic data indicate that quinapril elimination is dependent on level of renal function in patients with heart failure and renal impairment. The recommended initial dose of quinapril is 5 mg in patients with creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance of 10 to 30 mL/min. There is insufficient data for dosage recommendation in patients with creatinine clearance less than 10 mL/min ([see Section 4.2 Dose and method of administration](#), [Congestive Heart Failure](#), [Section 4.4 Special warnings and precautions for use](#) and [Section 4.5 Interaction with other medicines and other forms of interaction](#)).

4.3 Contraindications

Quinapril is contraindicated in:

- Patients who are hypersensitive to quinapril or any of the other ingredients in the tablet.
- Patients with history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor.
- Concomitant use with sacubitril/valsartan due to the increased risk of angioedema.
- Severe renal artery stenosis.
- Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes. These patients are likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore not be used. In such patients, the use of either alternative antihypertensive drugs or alternative membranes (eg. cuprophane or polysulphone PSF) for haemodialysis is recommended.
- Patients with dynamic left ventricular outflow obstruction.
- Pregnancy ([see Section 4.6 Fertility, pregnancy and lactation](#)). Women who intend to become pregnant, or of childbearing potential unless on an effective contraceptive and highly unlikely to conceive.
- Patients with diabetes or with renal impairment ($GFR < 60 \text{ mL/min/1.73m}^2$), who are being treated the direct renin inhibitor, aliskiren.

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4.4 Special warnings and precautions for use

Hypersensitivity/Angioedema

Angioedema has been reported in patients treated with angiotensin-converting enzyme inhibitors. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment 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; 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 therapy e.g., subcutaneous adrenaline solution 1:1000 (0.3 to 0.5 ml) should be promptly administered.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see Section 4.3 Contraindications).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of this medicinal product. Treatment with this medicinal product must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see Section 4.3 Contraindications and Section 4.5 Interaction with other medicinal products and other forms of interaction).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see Section 4.5 Interaction with other medicinal products and other forms of interaction). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there has been no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Ethnic Differences

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.

Sensitivity reactions

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma, eg. purpura, photosensitivity, urticarial, necrotising angitis, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions.

Hypotension

Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with Accupro but it is a possible consequence of ACE inhibitor therapy particularly in salt/volume depleted patients such as those previously treated with diuretics, who have a dietary salt reduction, who are on dialysis, have diarrhoea or vomiting or have severe renin-dependent hypertension. 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.

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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 2 weeks of treatment and whenever the dosage of quinapril is increased.

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

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

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

Anaphylactoid Reactions During Desensitization

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

Anaphylactoid Reactions During LDL Apheresis

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

Anaphylactoid Reactions During Haemodialysis

Clinical evidence has shown that patients haemodialysed using certain high-flux membranes (such as polyacrylonitrile membranes) are likely to experience anaphylactoid reactions with concomitant ACE inhibitor treatment. This combination should therefore not be used ([see Section 4.3 Contraindications](#)). The use of either alternative antihypertensive drugs or alternative membranes for haemodialysis is recommended.

Impaired Renal Function

In patients with renal insufficiency, monitoring of renal function during therapy should be performed as deemed appropriate, although in the majority renal function will not alter or may improve.

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 azotaemia and rarely acute renal failure and/or death ([see Section 4.8 Undesirable Effects](#)).

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 usually 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.

ACE inhibitors should not be used in patients with known or suspected renal artery stenosis ([see Section 4.3 Contraindications](#)). When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the

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artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <60 mL/min require a lower initial dosage of quinapril ([see Section 4.2 Dose and method of administration](#)). These patients' dosage should be titrated upwards based upon therapeutic response, and renal function should be closely monitored although initial studies do not indicate that quinapril produces further deterioration in renal function.

In people with a creatinine clearance < 40 mL/min/1.73 m², quinaprilat did accumulate but not as much as would be suggested by the increased half life (2.2 hours to 12 hours) implying that alternative methods of removal become important.

Some patients with hypertension or heart failure with no apparent pre-existing renal disease have developed increases (>1.25 times the upper limit of normal) in blood urea nitrogen and serum creatinine, usually minor and transient, especially when quinapril has been given concomitantly with a diuretic. Increases in blood urea nitrogen and serum creatinine have been observed in 2% and 2%, respectively of hypertensive patients on quinapril monotherapy and in 4% and 3%, respectively of hypertensive patients on quinapril/HCTZ. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or quinapril may be required.

There is insufficient experience in patients with severe renal impairment (creatinine clearance <10 mL/min). Treatment is therefore not recommended in these patients.

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

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

Evaluation of hypertensive patients should always include assessment of renal function ([see Section 4.2 Dose and method of administration](#)).

Haemodialysis and LDL Apheresis:

Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for haemodialysis. Similar reactions have been observed during low density lipoprotein apheresis with dextran-sulphate. This method should therefore not be used in patients treated with ACE inhibitors.

Impaired Hepatic Function:

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 de-esterification of quinapril.

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Rarely, ACE inhibitors have been associated with a syndrome beginning as a cholestatic jaundice and progressing to a fulminant hepatic necrosis (in some cases fatal). Patients who during ACE inhibitor therapy experience jaundice or clearly elevated hepatic enzymes should discontinue quinapril and receive appropriate medical follow-up.

Cough

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

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

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

Hypoglycaemia and Diabetes

In diabetic patients ACE inhibitors may enhance insulin sensitivity and have been associated with hypoglycaemia in patients treated with oral antidiabetic agents or insulin. Glycaemic control should be closely monitored particularly during the first month of treatment with an ACE inhibitor (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Hyperkalaemia and Potassium-sparing Diuretics

ACE inhibitors decrease the formation of angiotensin II, which results in decreased production of aldosterone and an increase in serum potassium levels (> 5.5 mEq/L). Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium sparing diuretics or potassium supplements and/or consuming potassium containing salt substitutes, or other drugs known to raise serum potassium levels. Diabetics, and elderly patients particularly, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may co-exist with hyperkalaemia. It is recommended that patients undergoing ACE inhibitor treatment should have serum electrolytes (including potassium, sodium and urea) measured from time to time. (See [Section 4.4 Special warnings and precautions for use](#) and [Section 4.5 Interaction with other medicines and other forms of interaction](#)). This is more important in patients taking diuretics. When administered concomitantly, quinapril may reduce the hypokalaemia induced by thiazide diuretics.

Hyponatraemia and Syndrome of Inappropriate Anti-diuretic Hormone (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.

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. Monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

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Desensitisation

Patients receiving ACE inhibitors during desensitising treatment with hymenoptera venom have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they have reappeared upon inadvertent re-challenge.

Dermatological Reactions

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

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

Taste Disturbance (Dysgeusia)

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

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

Surgery/anaesthesia

In patients undergoing major surgery or who require anaesthesia with agents that produce hypotension, quinapril may 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 (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Serum potassium

Hyperkalaemia may occur during treatment with an ACE inhibitor. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, hypoaldosteronism.

ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, or in patients taking other active substances associated with increases in serum potassium (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalaemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Valvular Stenosis

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

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

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

Dual Blockade of the Renin-angiotensin-aldosterone System (RASS)

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

Do not co-administer aliskiren with quinapril in patients with diabetes or in patients with renal impairment (GFR<60 ml/min/1.73m²) ([see Section 4.3 Contraindications](#))

Use in the Elderly

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of quinapril where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Paediatric Use

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

4.5 Interaction with other medicines and other forms of interaction

Concomitant diuretic therapy

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients on diuretics, especially those on recently instituted diuretic therapy or in those with intravascular volume depletion, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with quinapril. The possibility of hypotensive effects with quinapril may be minimised by discontinuing the diuretic and ensuring adequate hydration and 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 and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised ([see Section 4.2 Dose and method of administration](#)).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with quinapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when quinapril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of quinapril with the above-mentioned medicines is not

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recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

In patients who are elderly or have compromised renal function, co-administration of an ACE inhibitor with sulfamethoxazole/trimethoprim has been associated with severe hyperkalaemia, which is thought to be due to trimethoprim. Quinapril and trimethoprim-containing products should therefore be co-administered with caution and with appropriate monitoring of serum potassium.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

Dual blockade of the RAAS with angiotensin receptors blockers, ACE inhibitors, or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. Closely monitor blood pressure, renal function and electrolytes in patients on quinapril and other agents that affect the RAAS ([see Section 4.4 Special warnings and precautions for use](#)).

Do not co-administer aliskiren with quinapril in patients with diabetes or in patients with renal impairment (GFR <60 mL/min/1.73 m²), in patients with hyperkalaemia (>5 mmol/L) or in congestive heart failure patients who are hypotensive ([see Section 4.3 Contraindications](#)).

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 co-prescribing quinapril and tetracycline or other drugs that interact with magnesium.

Surgery/anaesthesia

Although no data are available to indicate there is an interaction between quinapril and anaesthetic agents that produces hypotension, caution should be exercised when patients undergo major surgery or anaesthesia since ACE 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 (see Section 4.4 Special warnings and precautions for use).

Lithium

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

Nonsteroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

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

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. Monitor renal function periodically in patients receiving quinapril and NSAID therapy.

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The antihypertensive effect of ACE inhibitors, including quinapril, may be attenuated by NSAIDs.

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and or concomitant DPP-IV inhibitor (e.g. vildagliptin) therapy may be at increased risk for angioedema. Caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor or a neutral endopeptidase inhibitor (see Section 4.3 Contraindications) in a patient already taking an ACE inhibitor.

Agents Affecting Sympathetic Activity

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

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.

Allopurinol, cytostatic and immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia (see Section 4.4 Special warnings and precautions for use).

Alcohol, barbiturates and narcotics

Potential of orthostatic hypotension may occur.

Other antihypertensive drugs

There may be an additive effect or potentiation.

Antacids

Antacids may decrease the bioavailability of quinapril.

Antidiabetic drugs (oral hypoglycaemic agents and insulin)

In diabetic patients ACE inhibitors may enhance insulin sensitivity and have been associated with hypoglycaemia in patients treated with oral antidiabetic agents or insulin. Glycaemic control should be closely monitored particularly during the first month of treatment with an ACE inhibitor (see Section 4.4 Special warnings and precautions for use).

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 co-administration 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.
- Co-administration of multiple 10 mg doses of atorvastatin with 80 mg quinapril resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

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4.6 Fertility, pregnancy and lactation

Pregnancy

Use in Pregnancy (Category D)

As with all ACE inhibitors, quinapril is contraindicated in pregnancy ([see Section 4.3 Contraindications](#)). Pregnancy should be excluded before starting treatment with quinapril and avoided during the treatment. If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. When pregnancy is detected, the ACE inhibitor should be discontinued as soon as possible and arrangements for further care should be made.

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

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

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

There have also been reports of prematurity, hypotension, renal system disorders (including renal failure), skull hypoplasia, oligohydramnios, limb contractures, craniofacial deformities, hypoplastic lung development, intrauterine growth retardation, patent ductus arteriosus, foetal death and/or death in the newborn in association with the maternal use of ACE inhibitors. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

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

Lactation

ACE inhibitors, including quinapril, are secreted in human milk to a limited extent. Because of the potential for serious reactions in nursing infants, quinapril should not be given to a nursing mother.

Fertility

There were no adverse effects on fertility or reproduction in rats at oral doses up to 100 mg/kg/day.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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The most frequently reported adverse reactions found in controlled clinical 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%).

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Not known	Agranulocytosis, haemolytic anaemia, neutropenia, thrombocytopenia
Immune system disorders	Not known	Anaphylactoid reaction
Metabolism and nutrition disorders	Common	Hyperkalaemia
Psychiatric disorders	Common	Insomnia
	Uncommon	Confusional state, depression, nervousness
Nervous system disorders	Common	Dizziness, headache, paraesthesia
	Uncommon	Transient ischaemic attack, somnolence
	Rare	Balance disorder, syncope
	Not known	Cerebrovascular accident
Eye disorders	Uncommon	Amblyopia
	Very rare	Vision blurred
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
Cardiac disorders	Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations
Vascular disorders	Common	Hypotension
	Uncommon	Vasodilatation
	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, cough
	Uncommon	Dry throat
	Rare	Eosinophilic pneumonia
	Not known	Bronchospasm. In individual cases, upper airways obstruction by angioedema (that may be fatal)
Gastrointestinal disorders	Common	Vomiting, diarrhoea, dyspepsia, abdominal pain, nausea
	Uncommon	Flatulence, dry mouth
	Rare	Glossitis, constipation, dysgeusia
	Very rare	Ileus, small bowel angioedema
	Not known	Pancreatitis*
Hepato-biliary disorders	Not known	Hepatitis, jaundice cholestatic
Skin and subcutaneous tissue disorders	Uncommon	Angioedema, rash, pruritus, hyperhidrosis
	Rare	Erythema multiforme, pemphigus, urticaria

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System Organ Class	Frequency	Undesirable effects
	Very rare	Dermatitis psoriasiform
	Not known	Stevens Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, alopecia, photosensitivity reaction. Skin disorders may be associated with pyrexia, muscle and joint pain (myalgia, arthralgia, arthritis), vascular inflammation (vasculitis), inflammation of serous tissues and certain changes in laboratory values (eosinophilia, leukocytosis and/or antinuclear antibody increased, red blood sedimentation rate increased).
Musculoskeletal, connective tissue and bone disorders	Common	Back pain, myalgia
Renal and urinary disorders	Uncommon	Renal impairment, proteinuria
Reproductive system and breast disorders	Uncommon	Erectile dysfunction
General disorders and administration site conditions	Common	Fatigue, asthenia, chest pain
	Uncommon	Generalised oedema, pyrexia, oedema peripheral
Investigations	Common	Blood creatinine increased, blood urea increased**
	Not known	Haemoglobin decreased, haematocrit decreased, decreases in haematocrit and WCXC, hepatic enzyme increased, blood bilirubin increased. In patients with a congenital G-6-PDH deficiency, individual cases of haemolytic anaemia have been reported
Infections and infestations	Common	Pharyngitis, rhinitis
	Uncommon	Bronchitis, upper respiratory tract infection, urinary tract infection, sinusitis

* Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

** Such increases are more likely to occur in patients receiving concomitant diuretic therapy than those on monotherapy with quinapril. These observed increases will often reverse on continued therapy.

Vasculitis and gynecomastia have been reported with other ACE inhibitors and it cannot be excluded that these unwanted effects are class specific.

Laboratory Findings

Haematology: [See Section 4.4 Special warnings and precautions for use](#)

Hyperkalaemia: [See Section 4.4 Special warnings and precautions for use](#)

Hyponatraemia: [See Section 4.4 Special warnings and precautions for use](#)

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.

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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

The oral LD₅₀ of quinapril range from 1440 to 4280 mg/kg in mice and rats.

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

Signs and Symptoms

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

Treatment

Treatment is symptomatic and supportive, consistent with established medical care. Hypotension would normally be treated by intravenous volume expansion, such as an infusion of normal saline. Persistent hypotension should be treated by established procedures. Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose.

No data are available to suggest physiological manoeuvres (eg. manoeuvres to change pH of the urine) that might accelerate elimination of quinapril and its metabolites would be effective.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

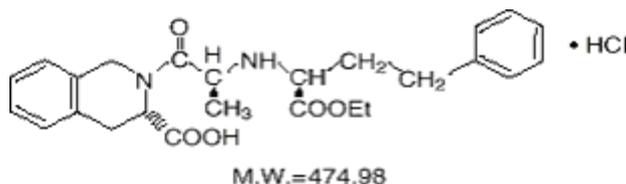
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-converting enzyme (ACE) inhibitor, ATC Code: C09AA06

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

Quinapril hydrochloride (CAS no. 82586-55-8) is chemically described as 2-(S)-[N-[[1-ethoxycarbonyl]-3-phenylpropyl]-3-phenylpropyl]-3-phenylpropyl-(S)-alanyl]-1,2,3,4-tetrahydro-3-(S)-isoquinolinecarboxylic acid, monohydrochloride.

It is chemically and pharmacologically related to enalapril. Its empirical formula is C₂₅H₃₀N₂O₅ · HCl and molecular weight is 475.0. Its structural formula is:



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

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Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, noradrenaline or adrenaline. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with quinapril alone resulted in mean increases in potassium of 0.07 mmol/L ([see Section 4.4 Special warnings and precautions for use](#)). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

Quinapril has been shown to be effective in the treatment of congestive heart failure and hypertension. While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. 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. Bradykinin acts on bradykinin receptors in the vascular endothelium to promote the release of the vasodilators such as nitric oxide and prostacyclin. Whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

ACE inhibitors, including quinapril, may enhance insulin sensitivity.

Endothelial Dysfunction

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

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

Clinical Effects

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 20-80 mg.

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Hypertension

Administration of 10 to 40 mg quinapril to patients with essential hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained throughout the 24-hour dosing interval and continue during long-term therapy with no evidence of tolerance.

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

Use of 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 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.

Heart Failure

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

5.2 Pharmacokinetic properties

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

Absorption

Following oral administration, peak plasma quinapril concentrations are observed within one hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is at least 60%. The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when quinapril tablets are administered during a high-fat meal.

Distribution

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

Metabolism

Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of 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.

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Elimination

Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose. It has an apparent elimination half-life in plasma of approximately 2 hours representing the clearance of the free quinaprilat from the plasma and a prolonged terminal phase with a half-life of 25 hours thought to reflect the slow release of quinaprilat from ACE.

Special Populations

Renal Impairment

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic haemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. A study in 20 patients with renal impairment (creatinine clearance 12 to 119 mL/min/1.73 m²) showed alterations in both quinapril and quinaprilat pharmacokinetics. The C_{max} and AUC for quinapril were greater in patients with renal impairment and the elimination half-life tended to be longer. However, these changes were small and probably not clinically important. The pharmacokinetic data for quinaprilat were markedly different. C_{max}, AUC and the elimination half-life all increased as renal impairment became greater. When the creatinine clearance was below 40 mL/min/1.73 m², trough levels of quinaprilat were markedly increased. The elimination half-life increased from 2 to 4 hours as creatinine clearance fell from 120 to 40 mL/min/1.73 m² and increased further to 12-14 hours when creatinine was 12 mL/min/1.73 m². Thus, if a person has a creatinine clearance below 40 mL/min/1.73 m², then it is likely that quinaprilat will accumulate and quinapril therapy should be started at a low dose and gradually titrated upward. If creatinine clearance is greater than 40 mL/min/1.73 m², quinapril and quinaprilat are unlikely to accumulate.

Hepatic Impairment

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

Cardiac Impairment

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

Elderly Patients (≥65 years)

Elimination of quinaprilat is reduced in elderly patients (≥65 years); this reduction is attributable to a decrease in renal function ([see Section 4.2 Dose and method of administration](#)) and not to age itself.

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

5.3 Preclinical safety data

Carcinogenicity

At least one other ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in man is unknown.

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Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign.

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day for 104 weeks. Female rats given the highest dose level have an increased incidence of mesenteric lymph node haemangiomas and skin/subcutaneous lipomas.

Genotoxicity

Neither quinapril nor quinaprilat are mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicological studies: In vitro mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleous test with mice, in vitro chromosome aberration with V79 cultured lung cells and an in vivo cytogenetic study with rat bone marrow.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium carbonate-heavy
Low-substituted hydroxypropyl cellulose
Crospovidone
Magnesium stearate
Drug Coat E 12.5%
Titanium dioxide
Talc
Macrogol 6000
Yellow iron oxide (5mg and 20mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blister packs of 30 and 90 tablets.

Not all pack types and pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

26 October 2006

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10. DATE OF REVISION OF THE TEXT

11 June 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3, 4.4, 4.5, 4.8	Updated safety information in accordance with Teva CCSI No. 303/07/01/19