SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kiprisil 5 mg film-coated tablet
Kiprisil 10 mg film-coated tablet
Kiprisil 20 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kiprisil 5 mg film-coated tablets:
Each film-coated tablet contains 5 mg quinapril (as quinapril hydrochloride).

Kiprisil 10 mg film-coated tablets:
Each film-coated tablet contains 10 mg quinapril (as quinapril hydrochloride).

Kiprisil 20 mg film-coated tablets:
Each film-coated tablet contains 20 mg quinapril (as quinapril hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Kiprisil 5 mg is an oval, biconvex, red-brown film-coated tablet, scored on both sides and imprinted with "I" on one side. Size 4.5 x 8.7 mm.
Kiprisil 10 mg is an oval, biconvex, red-brown film-coated tablet, scored on both sides and imprinted with "L" on one side. Size 5.8 x 11.3 mm.
Kiprisil 20 mg is a round, biconvex, red-brown film-coated tablet, scored on both sides and imprinted with "I" on one side. Diameter 7 mm.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension
Congestive heart failure

4.2 Posology and method of administration

The dose should be individualised
For the different dosage regimens Kiprisil is available in strengths of 5 mg, 10 mg, and 20 mg.

Essential Hypertension
Monotherapy: The recommended initial dose is 10 mg once daily. The dose may be subsequently adjusted, depending on the clinical response. Dose adjustment should be at 3 week intervals. The usual maintenance dose is 10-20 mg/day. The daily dose should not exceed 40 mg.
Quinapril should be given as a single dose or in two divided doses. Most patients can be managed with one daily dose.

Concomitant diuretic therapy
A dose of 2.5 mg should be given initially to determine the hypotensive effect. The dose should subsequently be adjusted until optimal response is achieved.

Congestive heart failure
Quinapril should be given as supplement to, or in combination with a diuretic and/or digitalis. Treatment may be initiated in outpatient care. However, in patients with severe heart failure, reduced renal function and a tendency to electrolyte disorder, treatment should be initiated in hospital. This is also applicable for concomitant treatment with other vasodilating agents. The patient should be carefully monitored during the first two weeks and whenever the dose of quinapril or diuretic is changed.

In order to closely monitor patients for symptomatic hypotension, a single 2.5 mg initial dosage is recommended. After this, patients should be titrated (allowing 2-3 weeks for dosage adjustment) to an effective dose (up to 40 mg/day) given in 1-2 doses. Patients are usually maintained effectively on doses of 10-20 mg/day given in 1-2 doses with concomitant therapy. The maximum dose of 40mg/day should not be exceeded.

If a satisfactory response has not been achieved within 3 months, a change in therapy should be considered.

Renal impairment and elderly patients (> 65 years):
The initial dose of quinapril should be reduced in patients with impaired renal function as the plasma concentration of quinaprilat increases with reduced creatinine clearance. As renal function tends to be reduced with age, this should also be taken into consideration in elderly patients. The following doses are recommended:

Creatinine clearance 30-60 ml/min:	initial dose 5 mg
	maintenance dose 5-10 mg
	maximum dose 20 mg
Creatinine clearance 10-30 ml/min:	initial dose 2.5 mg
	maintenance dose 2.5 mg
	maximum dose 5 mg

The interval between the doses should be not less than 24 hours because of the prolonged half life.

There is currently no information available about patients with creatinine clearance below 10 ml/min.
Dialysis has no appreciable effect on the elimination of quinaprilat.
If a satisfactory response has not been achieved within 3 months, a change of therapy should be considered.

Paediatric population
Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

- Hypersensitivity to quinapril, to any of the excipients listed in section 6.1 or any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Quinapril should not be used in patients with dynamic left ventricular outflow obstruction

4.4 Special warnings and special precautions for use

Quinapril should be used with caution in selected patients with aortic stenosis.

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

Symptomatic hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving quinapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and 4.8).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, should 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.

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

Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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.

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). 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.

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 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 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. These increases are 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.

Angioedema
Angioedema has been reported in patients treated with angiotensin-converting enzyme inhibitors. If laryngeal stridor or angioedema of the face, tongue, or glottis occur, 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).

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.

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.

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.

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

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
There is no experience regarding the administration of quinapril in patients with impaired hepatic function or progressive liver disease. Treatment with quinapril is therefore not recommended.

Quinapril when combined with a diuretic should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. The metabolism of quinapril to quinaprilat is normally dependent upon hepatic esterase.
Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril.

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. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia
In patients undergoing major surgery or during 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).

Hyperkalaemia and Potassium-sparing Diuretics
Patients on quinapril alone may have increased serum potassium levels. When administered concomitantly, quinapril may reduce the hypokalemia induced by thiazide diuretics. Because of the risk of further potentiating increases in serum potassium it is advised that combination therapy with potassium-sparing diuretics be initiated with caution and the patient's serum potassium levels be closely monitored (see Hypotension above and Section 4.5 Interaction with other medicinal products and other forms of interaction).

Diabetic patients
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).

Kidney transplantation
There is no experience regarding the administration of quinapril in patients with a recent kidney transplantation. Treatment with quinapril is therefore not recommended.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor treatment is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Tetracycline and other medicinal products that interact with magnesium

Because of the presence of magnesium carbonate in the formulation, quinapril has been shown in healthy volunteers to reduce the absorption of tetracycline in concomitant administration by 28-37%. This interaction should be considered if co-prescribing quinapril and tetracycline.

Concomitant diuretic therapy

Patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Quinapril. Hypotensive effects after the first dose of quinapril may be minimized by discontinuing the diuretic a few days prior to initiation of therapy. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced. In patients in whom a diuretic is continued, medical supervision should be provided for up to two hours after the initial dose of quinapril (see section 4.2 and 4.4).

Agents increasing serum potassium

Quinapril is an angiotensin-converting enzyme inhibitor capable of lowering aldosterone levels, which in turn can result in elevation in serum potassium. Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should be used with caution and with appropriate monitoring of serum potassium.

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 angiotensin converting enzyme inhibitors have been shown to block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion (see section 4.4).

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy due to the sodium-losing effect of these agents. Quinapril and lithium should be co-administered 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.

Non-steroidal anti-inflammatory drugs

In some patients, the administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of ACE inhibitors. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible and occur especially in patients with compromised renal function.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (e.g. 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.).

Alcohol, barbiturates or narcotics

Potentiation of orthostatic hypotension may occur.

Other anti-hypertensive agents

There may be an additive effect or potentiation.

Other agents

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.

Antacids

May decrease the bioavailability of quinapril.

Antidiabetic medicinal products (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). .

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitors therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section

5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation
Limited pharmacokinetic data demonstrate very low concentrations in breast milk *(see section 5.2)*. Although these concentrations seem to be clinically irrelevant, the use of Kiprisil in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.
In the case of an older infant, the use of Kiprisil in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

The ability to engage in activities such as operating machinery or operatin***g*** a motor vehicle may be impaired, especially when initiating quinapril therapy as occasionally dizziness or tiredness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with quinapril and other ACE inhibitors with the following frequencies:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

The most frequently adverse reactions found in clinical trial 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	***Undesirable effect***
Blood and the lymphatic system disorders	
Not known	Agranulocytosis, haemolytic anaemia neutropenia, thrombocytopenia
Immune system disorders	
Not known	Anaphylactic 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 attacks, somnolence
Rare	Balance disorder, syncope, neuropathy
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	Vasodilation
Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough, pharyngitis, rhinitis
Uncommon	Sinusitis, upper respiratory tract infection, bronchitis
Rare	Eosinophilic pneumonitis, worsening of asthma
Not known	Bronchospasm In individual cases, upper airways obstruction by angioedema (that may be fatal)
Gastrointestinal disorders	
Common	Vomiting, diarrhea, dyspepsia, abdominal pain nausea
Uncommon	Flatulence, dry mouth or throat
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,
Very rare	Dermatitis psoriasiformi
Not known	Stevens Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, alopecia, photosensitivity reaction. Skin changes may be associated with pyrexia, muscle and joint pain (myalgia, arthralgia, arthritis), vascular inflammation (vasculitis), inflammations of serous tissues and certain changes in laboratory values (eosinophilia,

	leucocytosis 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, urinary tract infection
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction
General disorders and administration site conditions	
Common	Fatigue, asthenia, chest pain
Uncommon	Generalised oedema, pyrexia, peripheral oedema
Investigations	
Common	Blood creatinine increased, blood urea increased **
Not known	Haemoglobin decreased, haematocrit decreased decreases in haemocrit 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

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

4.9 Overdose

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

No specific information is available on the treatment of over dosage with quinapril. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion.

Treatment is symptomatic and supportive, consistent with established medical care.

Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

5. PHARMACEUTICAL PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, ATC code: C09AA06
Kiprisil contains the hydrochloride salt of quinapril. The substance has three chiral centres and is a pure stereoisomer.

Quinapril is a prodrug, which is hydrolysed to the active metabolite quinaprilat, a potent long-acting inhibitor of angiotensin converting enzyme (ACE) in plasma and tissue. ACE catalyses the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. Inhibition of ACE results in decreased concentrations of angiotensin II and reduced aldosterone secretion; bradykinin metabolism is probably also inhibited. In clinical studies quinapril has been found to be lipid neutral and has no negative effect on glucose metabolism. Quinapril reduces the total peripheral and renal arterial resistance.
In general there are no clinically relevant changes in renal blood flow or glomerular filtration rate. Quinaprilat results in a reduction of prone, sitting and standing blood pressure. The peak effect is achieved after 2-4 hours at recommended doses. Achievement of maximum blood pressure lowering effect may require 2-4 weeks of therapy in some patients.
Morbidity/mortality data is lacking.

Quinapril can, if necessary, be co-administered with other blood pressure reducing agents. Concomitant treatment with thiazide diuretics increases the blood pressure lowering effect of quinapril.

Paediatric population
A randomized clinical trial using target doses of 2.5, 5, 10 and 20 mg of quinapril, in 112 children and adolescents with hypertension or high normal blood pressure over 8 weeks (2 weeks double blind and 6 weeks extension), failed to reach its primary objective of reduction of diastolic blood pressure after 2 weeks. For systolic blood pressure (secondary objective of efficacy) at Week 2 only there was a statistically significant linear dose response across treatments with a significant difference between the quinapril 20 mg QD and placebo treatment groups.

Long term effects of quinapril on growth, puberty and general development have not been studied.

5.2 Pharmacokinetic properties

The bioavailability of the active metabolite, quinaprilat, is 30-40% of the given oral dose of quinapril. Peak plasma concentrations are reached after approximately 2 hours. The absorption of quinapril is not affected by concurrent food intake, but an extremely high fat content in the food may reduce uptake. Approximately 97% of the drug is bound to plasma proteins. With repeat dosing quinaprilat has a half life of 3 hours. Steady state is reached in 2-3 days. Quinaprilat is mainly excreted unchanged by the kidneys. The clearance is 220 ml/min. Dialysis does not noticeably affect the elimination of quinapril. In patients with renal impairment, quinapril has not been detected in the dialysate and for the metabolite quinaprilat approximately 2.5% of the dose has been detected after peritoneal dialysis and 5.4% after haemodialysis.
Prolonged half life and increased concentration of quinaprilat in plasma occurs in patients with renal impairment (see 4.2 Posology and method of administration). In patients with

severe hepatic impairment a reduced concentration of quinaprilat is seen due to reduced hydrolysis of quinapril.

Paediatric population
The pharmacokinetics of quinapril has been studied in a single dose study (0.2 mg/kg) in 24 children aged 2.5 months to 6.8 years and a multiple dose study (0.016-0.468 mg/kg) in 38 children aged 5-16 years old, weighing 66-98 kg on average.

As in adults, quinapril was rapidly converted to quinaprilat. Quinaprilat concentrations generally peaked 1 to 2 hours post dose and declined with a mean half-life of 2.3 hours. In infants and young children the exposure following a single 0.2-mg/kg dose is comparable to that observed in adults after a single 10-mg dose. In a multiple dose study in school age and adolescents, the AUC and Cmax values of quinaprilat were observed to increase linearly with increasing dose of quinaprilat on a mg/kg basis.

Lactation
After a single oral dose of 20 mg of quinapril in six breast-feeding women M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5 µg/L) at all time points. It is estimated that a breastfed infant would receive about 1.6% of the maternal weight-adjusted dosage of quinapril.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that quinapril has no negative effects on fertility and reproductive performance in rats, and is not teratogenic. ACE inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core
Heavy magnesium carbonate
Calcium hydrogen phosphate, anhydrous
Pregelatinised starch (maize)
Croscarmellose sodium
Magnesium stearate

Film coating
Hypromellose
Hydroxypropylcellulose
Titanium dioxide (E 171)
Macrogol 400
Red iron oxide (E 172)
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
2 years.

6.4 Special precautions for storage
Do not store above 25 ˚C.

6.5 Nature and content of container
Blister (Al/Al/ Polyamide/PVC) containing 10, 14, 28, 30, 50, 56, 98, 100 and 500 (5 x 100) tablets.
Tablet container (polypropylene) containing 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
HEXAL AG
Industriestrasse 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)
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20 mg: 19703

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24 Oct 2003

10. DATE OF REVISION OF THE TEXT
2012-12-07