Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Quinapril 40 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg quinapril (as quinapril hydrochloride).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Yellow, oval film-coated tablet debossed “40” on one side and with a score line on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of essential hypertension
- Treatment of congestive heart failure

4.2 Posology and method of administration

For oral use.

The dose should be individualised.

For the different dosage regimens, appropriate strengths of quinapril are available.

Adults

Essential hypertension

Monotherapy: The recommended initial dosage is 10 mg once daily in hypertension. Depending upon clinical response, patient's dosage may be titrated (by doubling the dose allowing 3-4 weeks for dosage adjustment) to a maintenance dosage of 20 to 40 mg/day given as a single dose or divided into 2 doses. Long-term control is maintained in most patients with a single daily dosage regimen.

The usual maximum maintenance dose is 40 mg/day. In clinical trials, some patients were treated with dosages up to 80 mg/day.

Concomitant Diuretics: Symptomatic hypotension may occur following initiation of therapy with quinapril. This is more likely in patients who are being treated currently with diuretics. Caution is therefore recommended, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2-3 days before beginning therapy with quinapril. In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of quinapril is recommended in patients who are being treated with a diuretic.
After this the dosage of quinapril should be titrated (allowing adequate time for dosage adjustment) to the optimal response *(see section 4.5).*

Congestive Heart Failure

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 or 2 doses with concomitant diuretic and/or cardiac glycoside therapy. Patients are usually maintained effectively on doses of 10-20 mg/day given in 1-2 doses with concomitant therapy. The maximum dose of 40 mg/day should not be exceeded.

Patients who are considered to be at higher risk should have treatment initiated in hospital *(see section 4.4).*

Elderly (>65 years)

As renal function tends to be reduced with age, this should also be taken into consideration in elderly patients. An initial dosage in essential hypertension of 2.5 mg is recommended followed by titration to the optimal response.

Renal impairment

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. The following initial doses are recommended:

Creatinine clearance (ml/min)	Maximum initial dose recommended (mg)
>60	10
30-60	5
10-30	2.5
<10	Insufficient experience

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 or to any other ACE inhibitor.

Pregnancy: Quinapril is contraindicated in the second and third trimester of pregnancy *(see sections 4.4 and 4.6).*

Quinapril is contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.

Quinapril is contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 Special warnings and precautions for use

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 section 4.8).* In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. 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.
If 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, which can be given without difficulty once the blood pressure has increased after volume expansion.

Patients who may be considered to be at higher risk and should have treatment initiated in hospital include patients who are on high dose loop diuretics (e.g. > 80 mg furosemide) or on multiple diuretic therapy, have hypovolaemia, hyponatraemia (serum sodium < 130 mgEq/l) or systolic blood pressure < 90 mm Hg, are on high dose vasodilator therapy, have a serum creatinine > 150 µmol/l or are aged 70 years or over.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, quinapril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis, subaortic stenosis or hypertrophic cardiomyopathy. In haemodynamically relevant cases quinapril should not be administered.

Renal function impairment including renal artery stenosis
In cases of renal impairment (creatinine clearance <60 ml/min), the initial quinapril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of quinapril therapy.
Some hypertensive patients with no apparent pre-existing renal 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 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) and in patients on dialysis. Treatment is therefore not recommended in these patients.

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.

Haemodialysis Patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

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

Desensitisation
Some patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including quinapril. Symptoms may appear long after initiation of treatment, at any time during therapy. In such cases, quinapril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema.

Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Caution should be exercised in those known to be hypersensitive to other ACE inhibitors, and particularly those with obstructive airways disease. 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).*

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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.

Neutropenia/Agranulocytosis
Neutropenia, agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Quinapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If quinapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Ethnic differences
ACE inhibitors cause a higher rate of angioedema in black patients. As with other ACE inhibitors, quinapril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

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.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including quinapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended *(see section 4.5).*

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 during the first month of treatment with an ACE inhibitor *(see section 4.5)*

Lithium
The combination of lithium and quinapril is generally not recommended *(see section 4.5).*

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).*

Primary hyperaldosteronism
Patients with primary hyperaldosteronism generally do not respond to antihypertensive agents acting via the renin-angiotensin-system. Therefore, treatment with ACE inhibitors is not recommended in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

Tetracycline
Because of the presence of magnesium salts in the formulation, quinapril has been shown in healthy volunteers to reduce the absorption of tetracycline in concomitant administration by 28-37%. It is recommended that concomitant administration with tetracycline be avoided.

Concomitant diuretic therapy
Patients treated with diuretics may occasionally experience an excessive reduction of blood pressure after initiation of therapy with quinapril. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose *(see section 4.2 and section 4.4).*

Agents increasing serum potassium
Quinapril is an angiotensin-converting enzyme inhibitor capable of lowering aldosterone levels, which in turn can result in a mild elevation in serum potassium. ACE inhibitors attenuate diuretic-induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see section 4.4), especially in patients with impaired renal function, since by decreasing aldosterone production, quinapril often causes an increase in 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.

Lithium
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy due to the sodium-losing effect of these agents.
These medicinal products 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 medicinal products including acetylsalicylic acid $\geq$ 3 g/day
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.

Allopurinol, cytostatic and immunosuppressive agents, systemic corticosteroids or procainamide
Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Alcohol, barbiturates, narcotics, tricyclic antidepressants or neuroleptics:
Potentiation of orthostatic hypotension may occur.

Other antihypertensive medicinal products
ß-blockers, methyldopa and diuretics may enhance the hypotensive effects of quinapril, and should only be used under careful supervision. Concomitant propranolol did not affect the pharmacokinetics of quinapril in a single dose study.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids
May decrease the bioavailability of quinapril.

Antidiabetic products (oral hypoglycaemic agents and insulin)
Concomitant administration of ACE inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. Dosage adjustments of the antidiabetic product may be required.

Trimethoprim
A severe hyperkalaemia has been reported during concomitant treatment of ACE-inhibitors with trimethoprim.

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 contraindicated during the 2nd and 3rd 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 inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 inhibitor 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 inhibitor 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 Quinapril 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 Quinapril 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

Quinapril has no or negligible influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur, especially at the

beginning of treatment or in combination with alcohol.

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, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10000, < 1/1000) very rare (<1/10000), including isolated reports.

Psychiatric disorders
Uncommon: Sleep disorders, nervousness
Rare: Depression, confusion

Nervous system disorders
Common: Dizziness
Uncommon: Paraesthesia, somnolence
Rare: Disturbances of balance, neuropathy.

Eye disorders
Rare: Blurred vision, amblyopia

Ear and labyrinth disorders
Rare: Tinnitus

Cardiac disorders
Uncommon: Palpitations, asystole, chest pain, angina pectoris
Rare: Tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage

Vascular disorders
Common: Hypotension
Uncommon: Postural hypotension

Blood and lymphatic disorders
Uncommon: Neutropenia
Rare: Agranulocytosis

Respiratory, thoracic and mediastinal disorders
Common: Cough
Uncommon: Sinusitis, pharyngitis, upper respiratory tract infection
Rare: Bronchospasm, dyspnoea, bronchitis, rhinitis, worsening of asthma
Very rare: Allergic alveolitis, anaphylactoid reaction

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea
Uncommon: Dyspepsia, abdominal pain, dry mouth or throat, flatulence
Rare: Altered taste, constipation, pancreatitis, glossitis, ileus

Hepato-biliary disorders
Rare: Hepatic function disturbance
Very rare: Cholestatic icterus, hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, rash, exfoliative dermatitis, increased perspiration, exanthema, urticaria
Rare: Erythema multiforme, Stevens Johnson syndrome, epidermic necrolysis, psoriasis-like efflorescences, alopecia, pemphigus, photosensitivity

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia, myalgia, back pain

Renal and urinary disorders
Uncommon: Proteinuria (sometimes with concurrent deterioration of kidney function)
Rare: Impairment of kidney function, hyperkalaemia
Very rare: Kidney failure

Reproductive system and breast disorders
Uncommon: Impotence

General disorders
Common: Headache, fatigue
Uncommon: Asthenia, vertigo,angioedema (swelling of the extremities, swelling of face, lips, tongue, pharynx, glottis and /or larynx)

Rare cases of agranulocytosis have been reported, and also a syndrome including fever, serositis, vasculitis, myalgia, arthralgia/arthritis, positive ANA-titre, SR-elevation, eosinophilia, and leukocytosis. Gynaecomastia and vasculitis have been reported with other ACE-inhibitors and it cannot be excluded that these unwanted effects are group specific.

Laboratory
Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 3% and 4% respectively of the patients on monotherapy. 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.
Slight decreases in haemoglobin and haematocrit values have been reported for other ACE-inhibitors. It cannot be excluded that these observations are group specific.

4.9 Overdose

Symptoms
Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

Treatment
Measures to prevent absorption (e.g. gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent. Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin-II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors
ATC Code: C09AA06

Quinapril 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. A decrease in left ventricular hypertrophy was observed with quinapril in experimental models of hypertension in animals. Morbidity/mortality data is lacking.

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

In 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 active substance 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 section 4.2). In patients with severe hepatic impairment a reduced concentration of quinaprilat is seen due to reduced hydrolysis of quinapril.

Lactation:

After a single oral dose of 20 mg of quinapril in six breast-feeding women, the 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.

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 halflife 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 quinapril on a mg/kg basis.

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:
Magnesium carbonate, heavy
Calcium hydrogen phosphate, anhydrous
Gelatin
Crospovidone Type A
Magnesium stearate

Film coat:
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Polyamide/aluminium/PVC - aluminium blisters. Supplied in packs of 28, 28 (calendar), 30, 50, 50 (hospital pack), 56, 100 or 300 (10x30) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.,
Computerweg 10
3542 Dr Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/8/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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