

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

Quinapril

Accupro, Accupril, Acuitel, Accuprel, Accuprin, Accupron

UK/W/013/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	24 March 2011
Date of finalisation of PAR	24 March 2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal products:	Accupro, Accupril, Acuitel, Accuprel, Accuprin, Accupron
INN (or common name) of the active substance(s):	Quinapril
MAH:	Pfizer Limited
Pharmaco-therapeutic group (ATC Code):	C09AA06
Pharmaceutical form and strengths:	5 mg, 10 mg, 20 mg, 40 mg film coated tablets

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I. EXECUTIVE SUMMARY

This is an assessment of data for quinapril, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 Jan 2007. The UK is Rapporteur for this procedure.

Quinapril is an angiotensin converting enzyme (ACE) inhibitor that is indicated for treatment of hypertension (high blood pressure) and congestive heart failure in adults. It has been in use since the early 90s through a National procedure at doses of 5, 10, 20 and 40mg. It does not have an approved paediatric posology in any country, and the extent of its off-label use is not known.

The current submission includes two clinical studies of quinapril in paediatric hypertension: an efficacy and a pharmacokinetic (PK) multiple dose study, a single dose PK study and a brief clinical overview. These studies have been conducted in response to a written request for paediatric data from the US food and drug administration (FDA) Paediatric Exclusivity list.

The efficacy data from the study 906-427/440 has been previously assessed by the FDA in 2002. It was also assessed by MHRA, followed by UK Expert advisory consultation in December 2004; concluding that efficacy has not been shown with respect to the primary efficacy end point of reduction in diastolic blood pressure. However in the UK, it was nationally recommended that changes should be made to sections 4.2 and 5.1, and in line with the summaries of product characteristics for other ACE inhibitors. The results of neither single (906-434) nor multiple dose (906-427/440) PK studies have been assessed before.

The first round of preliminary assessment has already been carried out and the preliminary assessment report (pages 6 – 31) was circulated on 20 January 2010. Comments and additional requests for information have been received from the other MS and a list of questions has been put to the Applicant. The assessment of the applicants response to the questions raised is in pages 31-40. On day 90 of the procedure, Rapporteur's conclusions, recommendation and proposed changes to SmPC were endorsed by all concerned MSs.

SmPC and PL changes are proposed in sections 5.1 & 5.2.

Summary of outcome

- No change
- Change
- New study data: summaries of efficacy & PK findings added to sections 5.1 & 5.2
- New safety information
- Paediatric information clarified
- New indication

II. RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy together with the assessment of the response to the list of questions raised by the Rapporteur and other MS, and taking into account the previous national assessment in the UK in Dec 2004, it is considered that the results of these studies do not support a paediatric posology. However, the incorporation of summaries of efficacy and PK findings in section 5.1, 5.2 and a cross reference in section 4.2 of the SmPC will be helpful to the prescriber.

The safety profile of quinapril generally resembles that of adults and no new adverse event (AE) or pattern of incidences in children has emerged as a result of the submitted data. No change to section 4.8 is required.

The following changes to the SmPC are recommended.

Proposed SmPC Changes

The following changes to the SmPC were proposed after assessment of the data and the MAH response (in italics and strike through):

Section 4.2:

~~Children and adolescents~~

~~There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above. (See section 5.1). There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.~~

Paediatric population

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

Section 5.1:

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), ~~a reduction in systolic blood pressure alone was noted across all treatment groups at the end of 2 weeks only. A dose response effect between groups was not seen. The reduction in diastolic pressure overall, and for each group was similar to placebo in these subjects suggesting that a dose response effect was not established.~~ *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.

Section 5.2:

~~A dedicated quinapril pharmacokinetic study was conducted in paediatric patients chronically maintained on ACE inhibitors, other than quinapril, rather than healthy infants and children. Quinapril was rapidly converted to quinaprilat. Dosing on a mg/kg basis resulted in quinaprilat AUC and C_{max} values that were generally comparable across the age range of patients in this study.~~

~~The overall mean AUC_{0-∞} was 993 ng·h/mL (range: 533-1523), and mean C_{max} was 260 ng/mL (range: 70.0-445.5). Quinaprilat CL/F correlated well with body size (body surface area or weight) and creatinine clearance (mL/min). Pharmacokinetic results after a 0.2 mg/kg dose in infants and children are comparable to those observed following a 10-mg dose in adults.”~~

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 C_{max} values of quinaprilat were observed to increase linearly with increasing dose of quinapril on a mg/kg basis.”

III. INTRODUCTION

This is an assessment of data for quinapril, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 Jan 2007. The UK is Rapporteur for this procedure.

Quinapril is an angiotensin converting enzyme (ACE) inhibitor that is indicated for treatment of hypertension (high blood pressure) and congestive heart failure in adults. It has been in use since the early 90s through a National procedure at doses of 5, 10, 20 and 40mg. The applicant has no intention to market the 2.5 mg and syrup utilised in these studies in the future. It does not have an approved paediatric posology in any country, and the extent of its off-label use is not known.

On 28th of August 2009, the MAH submitted two completed paediatric studies for quinapril, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The current submission includes two clinical studies of quinapril in paediatric hypertension: an efficacy and a pharmacokinetic (PK) multiple dose study, as well as a single dose PK study. These studies have been conducted in response to a written request for paediatric data from the US food and drug administration (FDA) Paediatric Exclusivity Granted list. A short critical expert overview and a literature review have also been provided.

The MAH stated that the submitted paediatric studies and the overall risk: benefit ratio does not support the use of quinapril to treat hypertension in the paediatric population. The first round of assessment was carried out and the preliminary assessment report (pages 6 - 31) was circulated on 20 January 2010. Following the CMS's comments, a list of question was sent to the applicant. The assessment of the applicant's response to the questions is on pages 31 - 40 of this document.

Review of the published literature

MEDLINE, EMBASE, BIOSIS, and Derwent Drug File were manually searched through 17 August 2009 for all clinical trials, case reports, and epidemiology studies with the following terms: quinapril OR accupril OR 85441-61-8.RN AND hypertension OR high ADJ blood ADJ pressure OR HTN OR HPN AND (adolescent OR adolescence OR '17' ADJ years OR under ADJ '18') AND (paediatric OR pediatrics OR paediatric OR paediatrics OR child OR children). The individual publications were then reviewed for relevance. An important caveat of the literature review is that it reflects current information available in the public domain, which may not reflect the totality of the data since not all reports are published. Blumer et al (3), a dedicated pharmacokinetic study, was conducted in paediatric patients chronically maintained on ACE inhibitors, other than quinapril, rather than healthy infants and children.

Assessor's comment: the review of the published literature, provided by the applicant is deficient of any information and fails to identify published articles and abstracts that are relevant to quinapril in a paediatric population.

IV. SCIENTIFIC DISCUSSION

Drug characteristics

Quinapril is an angiotensin converting enzyme (ACE) inhibitor. The mode of action of quinapril in humans and animals is to inhibit circulating and tissue ACE activity, thereby decreasing vasopressor activity and aldosterone production. It is a prodrug which is de-esterified after absorption to form the active metabolite quinaprilat. The recommended therapeutic dose range in adults is 10-40 mg once/twice daily. In adults quinapril is indicated for treatment of hypertension and congestive heart failure as a monotherapy or in combination with diuretics. Currently, quinapril is not recommended in the European Union for use in children or adolescents below the age of eighteen due to insufficient data on safety and efficacy.

Quinapril is a rapidly converted to the active metabolite quinaprilat by ubiquitous nonspecific esterases. Elimination is primarily renal and clearance slightly exceeds glomerular filtration rate. Because quinaprilat is 97% protein bound, renal secretion is the predominant pathway.

Paediatric hypertension

Hypertension is an important risk factor for cardiovascular morbidity and mortality and occurs in 1 to 9% of children and adolescents. In younger children, hypertension is generally secondary to renal or renovascular disease. The most common cause of paediatric hypertension, accounting for between 60 and 70% of cases is renal disease, including hereditary kidney disorders, renal hypo- or dysplasia and acquired glomerulopathies. Other causes include diabetes mellitus, cardiac pathologies, coarctation of the aorta, and endocrine disease such as pheochromocytoma and hyperthyroidism. Essential hypertension is rare in infants and young schoolchildren, but is more common in adolescents. Its increasing prevalence during childhood parallels that of obesity. In adolescents, essential hypertension is more prominent, especially in association with obesity.

Hypertension in children is defined as diastolic and/or systolic blood pressure (BP) greater than the 95th percentile for gender, age and height, measured on at least 3 occasions. The treatment goal is generally to reduce BP to below the 95th percentile, although in some cases, e.g. children with nephropathy, a lower target may be desired.

Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics. There are currently a few drugs approved for the treatment of hypertension in children, but often the use of antihypertensives in this age group is off-label.

The submitted study was conducted to investigate the safety and efficacy of quinapril in the treatment of school age and adolescent paediatric patients who had mild to moderate hypertension (patients with DBP or SBP \leq 90th percentile for age, gender, and height).

Regulatory Background

The efficacy data from the study 906-427/440 has been previously assessed by the FDA in 2002. It was also assessed by MHRA, followed by UK Expert advisory consultation in December 2004; concluding that efficacy has not been shown with respect to the primary efficacy end point of reduction in diastolic blood pressure. However in the UK, it was nationally recommended that changes should be made to sections 4.2 and 5.1, and in line with the summaries of product characteristics for other ACE inhibitors.

The results of neither single (906-434) nor multiple dose (906-427/440) PK studies have been assessed before.

IV.1 Information on the pharmaceutical formulation used in the studies

Quinapril HCl brown film-coated round tablets (5 mg, 10 mg and 20 mg) used in these Paediatric clinical investigations. The tablets are claimed to be qualitatively and quantitatively identical to those of the marketed product, with the exception of the appearance of the tablets which do not contain debossing or engraving. Quinapril HCl was provided as tablets in dosage strengths of 2.5 mg, 5 mg, 10 mg and 20 mg, and as a syrup in a dosage strength of 1.0 mg/mL.

The quinapril HCl syrup formulation was prepared from bulk quinapril HCl. In this 50 mL syrup formulation, quinapril hydrochloride equivalent to 50 mg of base was dissolved in 10 mL of USP Purified Water. Simple Syrup (85% [w/w] sucrose in purified water, with 0.1% sodium benzoate as preservative) to adjust to the 50 mL volume. The combination was mixed thoroughly before use. Study medication was provided to the clinical sites for preparation.

The efficacy and safety study 906-427/440 utilized commercially approved strengths as well as an additional 2.5 mg tablet. The pharmacokinetic study 902-434 utilized quinapril HCl syrup. Quinapril 2.5 mg tablet and HCl syrup are not currently marketed strengths and formulation. The MAH does not intend to market the 2.5 mg tablet, or the quinapril HCl syrup.

IV.2 Clinical aspects

The MAH submitted final reports for:

- Study 906-434: A Study of the Pharmacokinetics of Quinapril in Paediatric Patients
- Study 906-427/440: An 8-Week, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Safety and Efficacy of Quinapril in Paediatric Patients with Hypertension (QUIK)

- Literature review based on several databases (Medline, Embase and Biosis)
- Quality overall summary
- Clinical over view

Clinical studies:

IV.2.1 Study 906-434: A Study of the Pharmacokinetics of Quinapril in Paediatric Patients

➤ Description

This open-label, single-dose pharmacokinetic study in paediatric patients (age 1 month to 6 years).

➤ Methods

- **Objective**

To characterize single-dose quinapril pharmacokinetics in paediatric patients (infants and children). The safety of a single dose of quinapril was also assessed in the stated population.

- **Study design**

Open-label, single-dose pharmacokinetic study in paediatric patients of either sex and any race, between 30 days to 6 years old (inclusive), and receiving an ACE inhibitor, were enrolled.

Blood samples (1.0 mL) were collected before and at 1, 2, 4, 8, 12, and 24 hours after the quinapril dose. Samples were stored at -20 degrees Centigrade and were later assayed for quinapril and quinaprilat.

To calculate a paediatric dose, it was assumed that renal elimination is proportional to glomerular filtration. For adults, the dose range is 10 to 80 mg of quinapril once a day. Using the lowest dose of 10 mg and scaling for glomerular filtration calculated by the Schwartz equation, an appropriate dose for infants and children was determined. Expressed on a weight basis, the calculated dose was approximately 0.2 mg/kg.

- **Study population /Sample size**

Twenty-four participants in this study were enrolled into 2 groups as follows:

Group 1: 11 patients from 2.5 to 23.2 months of age

Group 2: 13 patients from 24.5 to 81.6 months of age

Nine patients were male and 15 were female. Overall, age and weight ranged from 2.5 to 81.6 months and from 3.7 to 31.4 kg, respectively.

- **Treatments**

Using the lowest dose of 10 mg and scaling for glomerular filtration calculated by the Schwartz equation, an appropriate dose for infants and children was determined to be 0.2 mg/kg.

All patients received a single oral 0.2-mg/kg dose of quinapril syrup (1.0 mg/mL) prepared from bulk drug, administered following a 2-hour fast. Medication was administered with a syringe calibrated to two-tenths milliliter.

Patients were required to fast for at least 2 hours before the dose and to remain fasting for 2 hours after the dose. Patients were allowed to consume water or dextrose 5% in water ad lib during the fasting period. Activity was not restricted for the patients. Patients were permitted to take naps in the post-dose period.

- **Outcomes/endpoints**

Pharmacokinetics: The primary endpoints were the following PK parameters for quinapril and quinaprilat:

- Apparent clearance (CL/F)
- Area under the plasma concentration-time curve (AUC) and total AUC.
- Maximum concentration (C_{max}).
- Time to maximum concentration (T_{max}).
- Apparent half-life (t_{1/2}).

Safety: Safety was evaluated by monitoring adverse events (AEs), vital signs changes from baseline in sitting blood pressure (BP) and heart rate (HR) and Laboratory measurements.

- **Statistical Methods**

Quinaprilat pharmacokinetic parameter values were estimated using standard noncompartmental methods. Descriptive statistics of parameters for each age group were examined for differences of potential clinical importance. Relationships between patient demographics and quinaprilat parameter values were examined to assist in dose recommendations for this patient population.

The parameters Body surface area (BSA), Creatinine clearance normalized for 1.73 m² body surface area (nCLcr), Creatinine clearance (CLcr), and Oral clearance (CL/F) normalized per weight and BSA were calculated using Microsoft Excel. The exact dose administered was used to calculate CL/F. Weight, height, and serum creatinine determined at Screening were used in the calculations.

➤ **Results**

- **Pharmacokinetic results**

Quinaprilat AUC and C_{max} values were similar across the age range of patients in this study, indicating exposure to quinaprilat was similar among infants and children between 2.5 and 82 months of age when quinapril was administered on a milligram per kilogram basis. The overall

mean AUC was 965 ng·hr/mL with individual values ranging from 349 to 1523 ng·hr/mL. Mean Cmax was 250ng/mL with individual values ranging from 14.1 to 445.5 ng/mL (see table 3).

Table 3- Summary of Quinaprilat Pharmacokinetic Parameter Values by Age Group (Months)

Parameter	Mean (%CV) Parameter Values			
	Group 1		Group 2	
	≥1 and <24 months		≥24 and <82 months	
N	11		13 ^a	
Age, months	12.4	(59.5)	51.8	(32.0)
Weight, kg	8.0	(36.8)	18.0	(32.6)
CLcr, mL/min	28.7	(42.0)	60.2	(31.6)
nCLcr, mL/min/1.73m ²	126	(27.8)	150	(25.5)
Cmax, ng/mL	232	(54.2)	266	(38.2)
tmax, hr	2.5	(84.4)	1.6	(56.1)
AUC(0-tl _{dc}), ng·hr/mL	879	(37.1)	922	(35.2)
AUC(0-∞), ng·hr/mL	923	(33.6)	1003	(26.6)
t _{1/2} hr	3.5	(114.7)	2.3	(34.9)
CL/F, mL/min	31.2	(36.9)	63.2	(31.6)
CL/F, mL/min/kg	4.2	(50.1)	3.5	(28.4)
CL/F, mL/min/m ²	85.2	(43.7)	89.2	(25.9)

The exposure (Cmax and AUC) to quinaprilat following oral quinapril dosing on a milligram per kilogram basis appears to be similar in infants and children. Administration of a single 0.2-mg/kg dose of quinapril resulted in an average AUC of 965 ng·hr/mL, which is comparable to that observed in adults after receiving a single oral quinapril dose of 10 mg, the recommended starting dose of quinapril. In 2 separate dose-ranging studies, administration of a single 10-mg dose of quinapril as either capsules or commercial tablets to 12 healthy adult volunteers resulted in mean Cmax and AUC values of 317 and 223ng/mL and 1062 and 803 ng.

A linear relationship was observed between quinaprilat oral clearance and CLcr, similar to the relationship observed in adults. This relationship was expected since quinaprilat is predominantly excreted intact via the kidneys. Nonrenal elimination of quinaprilat is negligible. In the present study, patients had normal renal function with normalized CLcr >60 mL/min/1.73 m², with the exception of one Patient.

Unadjusted creatinine clearance is dependent on the age of the child. Dosage adjustment is recommended in adults with renal impairment. Similarly, dosage adjustment is indicated in paediatric patients with a normalized creatinine clearance <60 mL/min/1.73 m².

Oral clearance increased with age. This relationship was seen after a linear regression analysis [slope of 0.738 mL/min per month of age and intercept of 22.7 mL/min (r = 0.784)]. Oral clearance values normalized for body weight were, similar across the age range.

Assessor comments: as quinapril is rapidly metabolised to its active metabolite, quinaprilat, the MAH has measured the latter, which is appropriate. The sample collection times for measuring quinaprilat PK values are acceptable. However, this single dose study provides only limited information.

The Cmax and AUC values of quinaprilat following a single 0.2 mg/kg dose of quinapril is comparable to that observed in adults after receiving a single oral quinapril dose of 10 mg, (adult starting dose). Furthermore the Cmax and AUC values of quinaprilat following oral quinapril

dosing on a milligram per kilogram basis appears to be similar in infants and children.

A linear relationship was observed between quinaprilat oral clearance and CL_{cr}, similar to adults. Quinaprilat seems to be predominantly excreted intact via the kidneys with negligible non-renal elimination. Similar clearance per kg and m² were seen across the population from 2.5 - 82 months of age.

The half life of quinaprilat was higher (3.5 hrs) in 1-24 months old compared to the older children (2.3 hr) and adults (2hr).

- **Safety results**

One serious adverse event was reported. Patient 2 died approximately 2 months after study completion due to sepsis. This was considered to be unrelated to quinapril. Five patients reported a total of 9 adverse events on the study. Adverse events included lung disorder [bibasilar crackles and coarse rhonchi] (2), tachycardia (2), larynx oedema [oedema around the tracheostomy tube] (1), rash (1), sputum increase (1), pain (1), and sepsis (1). One of the episodes of tachycardia were considered to be possibly related to the study drug.

Physical examinations were performed during Screening, on Day 1, and at Closeout (Day 2). Vital signs including Sitting blood pressure (systolic and diastolic) and heart rate were assessed at Screening; predose on Day 1; and postdose at 10, 20, 30, 40, and 50 minutes, and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 8, 12, and 24 hours. Respiratory rate was recorded during screening and on Day 1 predose. There were no clinically significant changes noted for blood pressure, pulse, or respiratory rate. Laboratory abnormalities were sporadic, transient, and unrelated to drug administration.

Assessor's comment: no particular concerns were found from this single dose study on the 24 patient's who were already on other ACE inhibitors.

IV.2.2 Study 906-427/440: An 8-Week, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Safety and Efficacy of Quinapril in Paediatric Patients With Hypertension (QUIK)

➤ Description

An 8-week, randomized, double-blind, placebo controlled study. This study consisted of 3 phases: (1) a single-blind placebo lead-in phase, (2) a 2-week placebo-controlled, double-blind treatment phase, and (3) a 6-week double-blind treatment extension phase (all patients receiving active treatment). Eligible patients were school age and adolescent paediatric patients age 5 to 16 years with mild to moderate hypertension. The study was carried out from 29Oct 1999 to 22 Aug 2001.

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory assessments, vital signs, and physical examinations were monitored and reported.

➤ **Methods**

• **Objective(s)**

The objectives of this study were to investigate the safety and efficacy, including dose response, of quinapril in the treatment of children between 5 and 16 years of age who had mild to moderate hypertension.

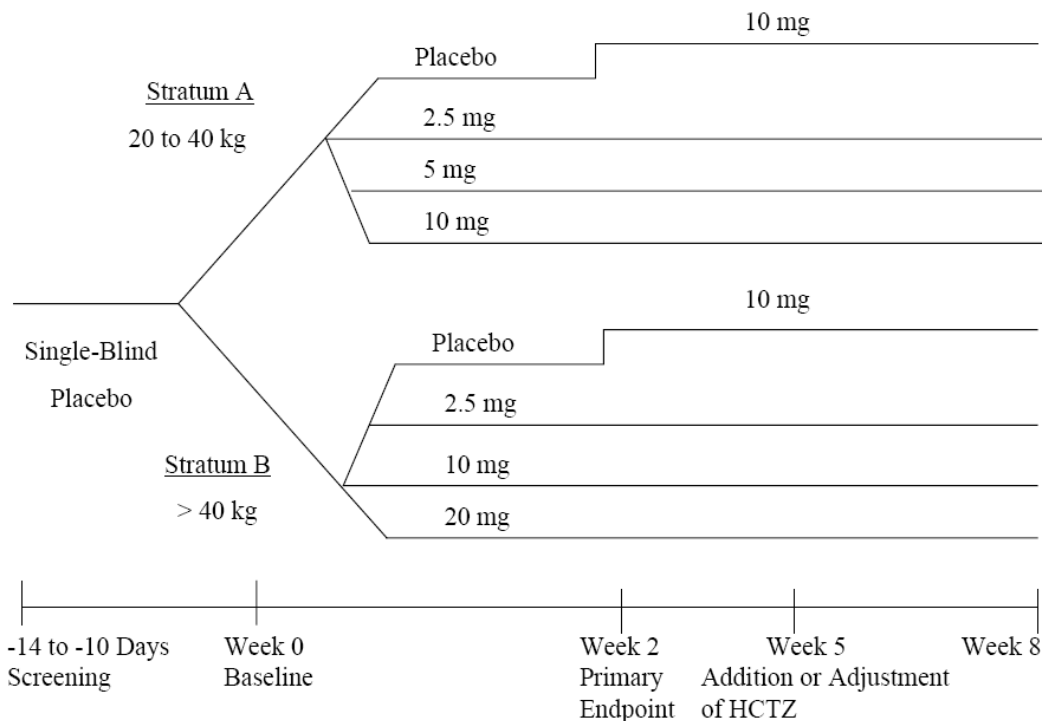
In a subset of patient quinapril concentration and quinaprilat pharmacokinetic parameters were determined.

Safety endpoints: adverse events, serious adverse events, clinical laboratory assessments, vital signs, and physical examinations were monitored and reported.

• **Study design**

This study consisted of 3 phases as shown in Figure 1, below:

Figure 1-



Phase 1: The single-blind placebo lead-in phase, to assess patients as candidates for the study, to take a medical history, perform a physical exam, determine Tanner Stage, and establish baseline laboratory values.

Phase 2: Patients were entered into the 2-week double-blind, placebo-controlled treatment phase and stratified into 1 of 2 dosing strata based on body weight (20-40 kg or >40 kg).

- Patients (n=19) in **Stratum A** (20-40 kg) were randomized to either placebo, quinapril 2.5, 5, or 10 mg once daily (QD) (1:1:1:1).

- Patients (n=93) in **Stratum B** (>40 kg) were randomized to either placebo, quinapril 2.5, 10, or 20 mg QD (1:1:1:1).

Phase 3: the 6-week double-blind extension phase, all patients were to receive active treatment by blinded cross-over from placebo. All quinapril-treated patients in both strata were to continue to receive quinapril at the same dose they had been randomized to for the 2-week double-blind treatment phase; all placebo-treated patients from both strata were to receive quinapril 10 mg QD. The change from placebo to quinapril 10 mg QD was done in double-blinded fashion.

Study medication was to be taken at the same time every day. Cuff BP was to be measured 3 times at each clinic visit with 3 minutes between each measurement.

Assessor's comments: the current study was designed and powered based on Study Design "A" of the FDA guidelines for paediatric studies in hypertension and is also in concurrence with EMEA 2009 guide lines.

Efficacy evaluations were based on auscultatory cuff measurement of SBP and DBP, with the primary efficacy parameter being the changes from baseline (week 0) to week 2 in DBP at trough (just prior to next dose).

- **Study population /Sample size**

Eligible patients were school age and adolescent paediatric patients age 5 to 16 years with mild to moderate hypertension. A total of 123 patients were screened for the study and 112 patients (59 [52.7%] school age and 53 [47.3%], adolescent) were included in the study. Gender distribution was 59.9% male and 41.1% female, and patients were racially diverse (white, 36.6%; black, 34.8%; Hispanic, 18.8%; Asian or Pacific, 2.7%; and other, 7.1%).

- **Treatments**

Doses were selected to approximate plasma levels in a range similar to that from the lowest approved adult dose to the maximally approved dose in adults and with consideration to investigator concerns related to the potential safety risks posed by higher doses. The dose range of 2.5 to 10 mg once daily for children weighing 20 to 40 kg and 2.5 to 20 mg once daily for children weighing >40 kg was decided. All patients received quinapril in tablet forms, with clinical or marketing image.

Patients completed a total of 8 weeks of treatment: 2 weeks of treatment with placebo, 2.5, 5, 10, or 20 mg quinapril and 6 weeks of active treatment with 2.5, 5, 10, or 20 mg quinapril depending on dose assignment. The dose and type of concurrent medications were kept unchanged throughout the screening and treatment phase of the study.

- **Outcomes/endpoints**

The primary efficacy parameter was the change in DBP from baseline (Week 0) to Week 2, measured at trough (just prior to next dose, non-peak as defined below) of the dosing interval.

The secondary efficacy parameters were:

- Change from baseline in DBP at Week 8
- Change from baseline in SBP at Weeks 2 & 8
- Change from baseline in mean arterial pressure (MAP) at Weeks 2 & 8, with MAP calculated as $2/3(\text{DBP}) + 1/3(\text{SBP})$
- Response status (yes/no); response defined as those patients with a 10 mm Hg drop in SBP, or a 5 mm Hg drop in DBP or reduction of SBP and DBP to <90th percentile for gender, age, and height, after 2 and 8 weeks of treatment
- Requirement (yes/no) of co administration or increase in dose of diuretic HCTZ for BP control
- Withdrawal (yes/no) due to lack of efficacy or AEs or serious adverse events (SAEs) by dose
- Response status (yes/no); response defined as reduction of SBP and DBP to <90th percentile for gender, age, and height measured at Weeks 2 and 8.

Blood samples were obtained at Week 2 at 0 hour (predose), 1, 2, 4, and 6 hours postdose in a subset of patients for determination of quinapril concentration and quinaprilat pharmacokinetic parameters.

Safety endpoints: Adverse events, serious adverse events, clinical laboratory assessments, vital signs, and physical examinations were monitored and reported.

• Statistical Methods

Determination of Sample Size

The sample size of 95 patients was expected to provide an 80% power to detect a quinapril dose response in DBP (slope = -1.45). This estimate of the sample size was based on a revised standard deviation of 7 mm Hg in DBP change and a significance level of 5%. All analyses were done using a 2-sided 5% level of significance.

Efficacy

The change in DBP was taken on patients with non-peak measurements only. Non-peak measurements were those BP measurements taken ≥ 8 hours from last dose; 'peak' measurements were those measurements taken <8 hours from last dose. An analysis of covariance (ANCOVA) model was used, which included treatment and weight strata as effects and baseline DBP as covariate. Additional ANCOVA models were performed to investigate the interaction of treatment with baseline and weight strata, and to investigate the effects of age, race, and gender. The effect of peak/nonpeak measurement was nonsignificant for both DBP ($p = 0.2453$) and SBP ($p = 0.3877$).

Secondary efficacy parameters were analyzed with an ANCOVA model that included all randomized patients having the secondary measurement of interest at baseline and at the time point of interest (Week 2 or 8). A trend test using appropriate linear contrasts was performed to determine the significance of the linear dose response. Change from baseline in DBP and SBP at Weeks 2 and 8 was analyzed using a regression analysis with mg/kg dose as the effect.

For both primary and secondary parameters a linear contrast was performed to determine the significance of the linear dose-response. If a significant linear dose response was noted, estimates from this model were used to compare each dose level with placebo using a step-down procedure from high to low dose. The method of last observation carried forward (LOCF) was not used in primary or secondary analyses.

Pharmacokinetics

The analyses were performed using a validated LC/MS/MS method at MDS Pharma Services. Quinaprilat pharmacokinetic parameters were determined using standard noncompartmental methods.

➤ Results

- Recruitment/ Number analysed

A total of 123 patients were screened for the study and 112 patients (59 [52.7%] school age and 53 [47.3%], adolescent) were randomized. Overall, 66 (58.9%) males and 46 (41.1%) females participated in the study. Similar percentages of patients were white (36.6%) and black (34.8); 18.8% were Hispanic, 2.7% were Asian, and 7.1% were listed as “other.”

To expand enrolment and enhance inclusion of patients of Hispanic origin, a second protocol (906-440) with study design identical to 906-427 was approved March 20, 2000, and was initiated at multiple sites in Central and South America. The studies are referred to as single study, 906-427/440, since the databases from these 2 studies were to be pooled for combined analysis; separate protocol numbers were issued for administrative purposes only.

- Baseline data

Demographic and baseline characteristics for all patients randomized by dose group are summarized in Table 4 below.

Table 4- Baseline Patient Characteristics (All Randomized Patients)

	Placebo ^a	2.5 mg Quinapril	5 mg Quinapril	10 mg Quinapril	20 mg Quinapril	All Doses ^b	All Patients
	N = 27	N = 29	N = 5	N = 27	N = 24	N = 85	N = 112
Gender, n (%)							
Male	13 (48.1)	15 (51.7)	5 (100.0)	15 (55.6)	18 (75.0)	53 (62.4)	66 (58.9)
Female	14 (51.9)	14 (48.3)	0 (0.0)	12 (44.4)	6 (25.0)	32 (37.6)	46 (41.1)
Race, n (%)							
White	8 (29.6)	8 (27.6)	3 (60.0)	10 (37.0)	12 (50.0)	33 (38.8)	41 (36.6)
Black	11 (40.7)	13 (44.8)	1 (20.0)	8 (29.6)	6 (25.0)	28 (32.9)	39 (34.8)
Hispanic	5 (18.5)	4 (13.8)	1 (20.0)	6 (22.2)	5 (20.8)	16 (18.8)	21 (18.8)
Asian or Pacific Islander	1 (3.7)	1 (3.4)	0 (0.0)	1 (3.7)	0 (0.0)	2 (2.4)	3 (2.7)
Other	2 (7.4)	3 (10.3)	0 (0.0)	2 (7.4)	1 (4.2)	6 (7.1)	8 (7.1)
Age Group n (%)							
School Age (≤ Tanner Stage 3)	11 (40.7)	16 (55.2)	5 (100.0)	16 (59.3)	11 (45.8)	48 (56.5)	59 (52.7)
Adolescent (>Tanner Stage 3)	16 (59.3)	13 (44.8)	0 (0.0)	11 (40.7)	13 (54.2)	37 (43.5)	53 (47.3)
Weight (kg)							
Mean (SE)	76.9 (5.52)	76.7 (6.79)	29.0 (1.50)	71.7 (6.27)	72.7 (4.70)	71.2 (3.49)	72.5 (2.96)
(SD)	28.68	36.57	3.36	32.57	23.02	32.20	31.35
Median	78.0	67.1	28.3	67.1	67.9	66.7	68.1
Min. Max	20.3, 130.0	24.0, 161.2	25.2, 32.7	19.0, 156.0	42.7, 135.0	19.0, 161.2	19.0, 161.2
Etiology of Hypertension n (%)							
Primary (essential)	21 (77.8)	26 (89.7)	3 (60.0)	18 (66.7)	19 (79.2)	66 (77.6)	87 (77.7)
Renal Disease	4 (14.8)	3 (10.3)	1 (20.0)	5 (18.5)	3 (12.5)	12 (14.1)	16 (14.3)
Coarctation of Aorta	1 (3.7)	0 (0.0)	0 (0.0)	2 (7.4)	1 (4.2)	3 (3.5)	4 (3.6)
Other	1 (3.7)	0 (0.0)	1 (20.0)	2 (7.4)	1 (4.2)	4 (4.7)	5 (4.5)

Avg. Systolic BP at Baseline (mm Hg)							
Mean (SE)	133.4 (2.17)	132.9 (1.62)	129.3 (7.78)	132.8 (2.24)	130.4 (2.07)	132.0 (1.14)	132.3 (1.01)
(SD)	11.25	8.74	17.40	11.62	10.13	10.56	10.69
Median	131.7	134.0	123.3	132.7	129.7	132.3	132.2
Min, Max	117.3, 157.7	114.7, 148.3	110.7, 156.0	110.0, 163.3	108.0, 158.0	108.0, 163.3	108.0, 163.3
Avg. Diastolic BP at Baseline (mm Hg)							
Mean (SE)	78.3 (2.60)	77.5 (2.01)	78.3 (9.64)	77.3 (2.06)	76.3 (1.98)	77.2 (1.20)	77.4 (1.10)
(SD)	13.50	10.84	21.55	10.72	9.68	11.08	11.66
Median	79.3	78.3	72.0	78.0	77.3	77.3	78.0
Min, Max	49.3, 121.7	54.7, 97.3	61.3, 116.0	55.0, 95.3	50.7, 95.3	50.7, 116.0	49.3, 121.7

The average SBP and DBPs were 132.3 and 77.4 mm Hg, respectively. The number and percentages of patients with blood pressures <90th percentile, from the 90th to the 95th percentile, and >95th percentile are shown in table 5 below.

Table 5- Baseline Blood Pressure Percentiles for All Randomized Patients [N (%) of Patients]

Parameter	>95 th Percentile	90 th -95 th Percentile	<90 th Percentile
SBP	93 (83)	11 (10)	8 (7)
DBP	42 (38)	18 (16)	52 (46)

One hundred four (93%) patients had SBP that was \geq 90th percentile. Sixty (54%) were \leq 90th percentile for DBP.

Assessor's comment: 93% of randomized patients had SBP that was greater than or equal to the 90th percentile, but nearly half of all randomized patients had DBP that was less than 90th percentile for gender, age and height at baseline. This makes the whole study futile and meaningless as the primary objective of reduction in DBP is tested in a population where almost half of them do not have raised DBP at the baseline. The applicant needs to justify the recruitment of patients with normal DBP for a study with primary objective of lowering DBP.

Further more 78% of patients had essential hypertension and only 22% of patients had secondary hypertension; as school age children are usually prone to secondary hypertension, this limits the clinical usefulness of the study.

- **Efficacy results**

Primary efficacy objective: Mean Change From Baseline in DBP at Week 2

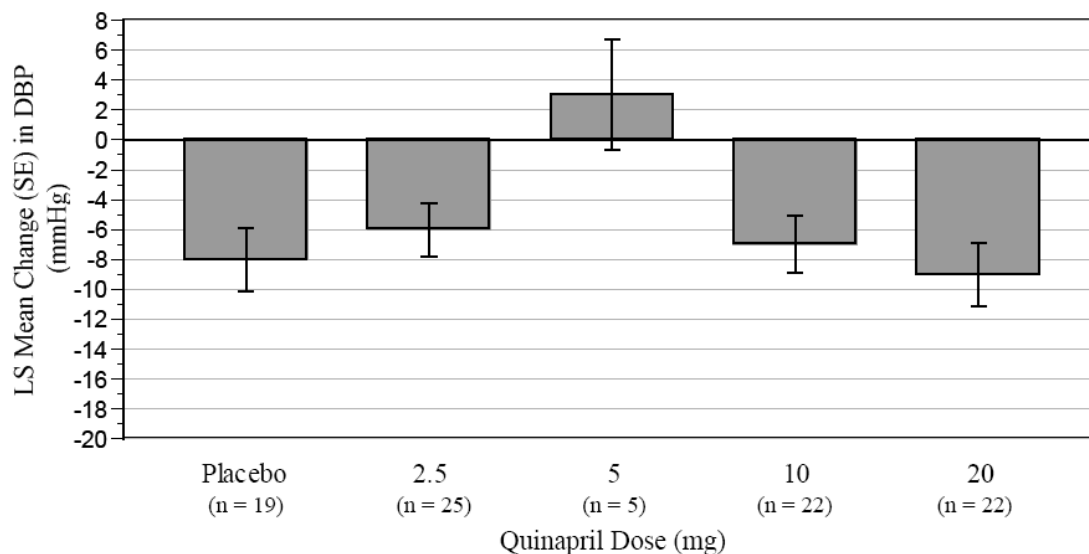
In the evaluation of DBP at Week 2, evaluable patients who had received active treatment (2.5, 5, 10, and 20 mg quinapril QD) had adjusted least squares mean changes in DBP of -6, 3, -7, and -9 mm Hg, respectively, compared with -8 mm Hg for the placebo group (table 6 and figure 2).

Table 6- Mean Change from Baseline in DBP at Week 2 [Mean (SE)] in (Evaluable Patients)

DBP (mm Hg)	Placebo N = 19	Quinapril mg QD				Linear Trend p-Value
		2.5 N = 25	5 N = 5	10 N = 22	20 N = 22	
n	19	25	5	22	22	
Baseline (Week 0)	80 (3.1)	78 (2.2)	78 (9.6)	76 (2.2)	77 (2.0)	
Week 2	75 (2.3)	74 (2.1)	77 (9.2)	72 (2.7)	72 (1.7)	
Mean Change	-5 (2.4)	-4 (2.1)	-1 (1.8)	-3 (1.2)	-5 (2.0)	
LS Mean Change ^b	-8 (2.1)	-6 (1.8)	3 (3.7)	-7 (1.9)	-9 (2.1)	0.0638

^a Patients with baseline and Week 2 nonpeak blood pressure measurement recorded ≥ 8 hours after last dose of study medication and with Week 2 visit occurring within IAP-defined time window.

Figure 2- Adjusted (LS) Mean Change From Baseline in DBP at Week 2. ($p = 0.0638$)



The dose response across the treatment groups did not demonstrate a statistically significant linear response ($p = 0.06$).

For the change in DBP, no testing was performed to detect differences between the placebo group and any of the active treatment groups due to the non-significant linear dose response across the treatment groups. Based on unadjusted pairwise comparisons of the quinapril doses there appeared to be a difference between the quinapril 5-mg dose group and each of the other active treatment groups (2.5, 10, and 20 mg quinapril groups). However, the results were influenced by the characteristics of the quinapril 5-mg dose group, which contained only a small number of patients ($n = 5$). A post hoc analysis, involving the removal of only 1 possibly discrepant patient with clinically paradoxical data from the 5 mg treatment group, demonstrated that these dose versus dose comparisons became nonsignificant.

No meaningful differences could be discerned between evaluable school age and adolescent populations with respect to mean change from baseline in DBP at Week 2.

Assessor's Comments: In the population tested, the efficacy of quinapril in all doses in reducing the DPB was equal or less than to placebo effect seen at the end of the 2 weeks blinded, placebo- controlled phase. There was no dose-response ratio established at the end of the 2 weeks. This total lack of observed efficacy is not surprising as nearly half of the population tested had DBP below the 90th percentile at the baseline.

Secondary efficacy objectives:

Change From Baseline in Systolic Blood Pressure at Week 2

In the evaluation of SBP at Week 2, all patients who had received active treatment (2.5, 5, 10, and 20 mg quinapril QD) had adjusted least square mean changes in SBP of -10, 1, -9, and -11 mm Hg, respectively, compared with -5 mm Hg for the placebo group (Table 7 and Figure 3). There was a statistically significant linear dose response for SBP across the treatment groups ($p = 0.02$) as well as significant difference between the placebo group and the quinapril 20 mg group, ($p = 0.02$).

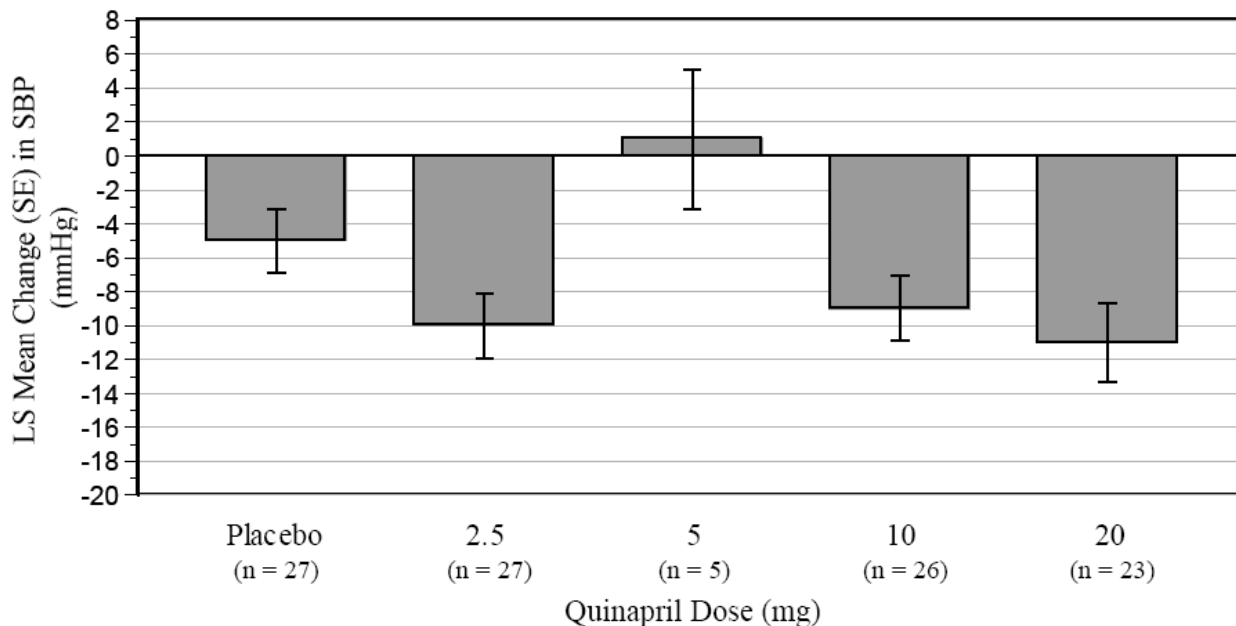
Table 7-Mean Change from Baseline in SBP at Week 2, a (All Patients) [Mean (SE)]

SBP (mm Hg)	Placebo N = 27	Quinapril mg QD				Linear Trend p-Value
		2.5 N = 29	5 N = 5	10 N = 27	20 N = 24	
n	27	27	5	26	23	
Baseline (Week 0)	133 (2.2)	133 (1.7)	129 (7.8)	133 (2.2)	131 (1.9)	
Week 2	131 (2.4)	125 (2.3)	128 (10.8)	127 (2.6)	124 (2.1)	
Mean Change	-2 (1.8)	-8 (1.9)	-2 (3.4)	-6 (1.3)	-7 (2.0)	
LS Mean Change ^b	-5 (1.9)	-10 (1.9)	1 (4.1)	-9 (1.9)	-11* (2.3)	0.0173

* Significantly different ($p = 0.0163$) from placebo

^a All patients with baseline and SBP measurement at Week 2 and visit occurring within IAP-defined time window.

Figure 3- Adjusted (LS) Mean Change From Baseline in SBP at Week 2 (All Patients) ($p = 0.017$)



Assessor's comment: Quinapril demonstrates efficacy in lowering SBP at 20mg dose group and

has a significant linear trend, because 83 % the population tested had elevated SBP above 95 percentile at the baseline.
 The discrepancies attributed to the quinapril 5-mg dose group (n = 5), seem to have no effect on the significant linear dose response.

Change from Baseline in Mean Arterial Pressure at Week 2 (All Patients)

In the evaluation of Mean Arterial Pressure (MAP) at Week 2, all patients who had received active treatment (2.5, 5, 10, and 20 mg quinapril QD) had adjusted least square mean changes in MAP of -7, 2, -7, and -10 mm Hg, respectively, compared with -7 mm Hg for the placebo group (Table 8). There was a statistically significant linear dose response for MAP across the treatment groups (p = 0.03). There were no statistically significant differences between the placebo group and any of the active treatment groups.

Table 8- Mean Change From Baseline in MAP at Week 2 a (All Patients) [Mean (SE)]

MAP (mm Hg)	Placebo N = 27	Quinapril mg QD				Linear Trend p-Value
		2.5 N = 29	5 N = 5	10 N = 26	20 N = 23	
n	27	27	5	26	23	
Baseline (Week 0)	97 (1.9)	96 (1.6)	95 (8.6)	96 (1.7)	95 (1.5)	
Week 2	92 (1.7)	92 (1.8)	94 (9.5)	91 (2.1)	89 (1.4)	
Mean Change	-5 (1.6)	-5 (1.7)	-1 (1.7)	-5 (1.2)	-6 (1.4)	
LS Mean Change ^b	-7 (1.5)	-7 (1.4)	2 (3.2)	-7 (1.5)	-10 (1.8)	0.0283

^a All patients with baseline and MAP measurement at Week 2 and visit occurring within IAP-defined time window.

Comparative Effects of Quinapril Doses on DBP, SBP, and MAP after 8 Weeks of Treatment

In the evaluation of the comparative effects of quinapril dose on DBP, SBP, and MAP after 8 weeks of treatment, a summarization of response between dose groups was performed for DBP, SBP, and MAP (Table 9). After 2 weeks of treatment all placebo patients received quinapril 10 mg once daily. Therefore, all patients had received active quinapril doses for Weeks 2 through 8.

Table 9- Mean Change from Baseline in DBP, SBP and MAP at Week 8 a (All Patients) [Mean (SE)]

	Quinapril 10 mg QD for 6 Weeks ^b N = 27	Quinapril mg QD			
		2.5 N = 29	5 N = 5	10 ^c N = 27	20 N = 24
DBP (mm Hg)					
n	27	26	5	26	21
Baseline	78 (2.6)	79 (2.1)	78 (9.6)	78 (2.1)	76 (2.2)
Week 8 ^d	69 (1.8)	71 (2.2)	74 (14.3)	71 (2.1)	69 (2.1)
Mean Change	-9 (2.1)	-7 (2.0)	-4 (5.5)	-7 (1.9)	-6 (2.2)
LS Mean Change ^e	-10 (2.0)	-8 (2.1)	-2 (4.4)	-8 (2.0)	-9 (2.5)
SBP (mm Hg)					
n	27	26	5	26	21
Baseline	133 (2.2)	134 (1.7)	129 (7.8)	133 (2.3)	131 (2.3)
Week 8 ^d	127 (2.5)	126 (2.2)	133 (12.3)	123 (2.8)	123 (3.0)
Mean Change	-6 (2.7)	-8 (1.8)	4 (5.1)	-10 (2.6)	-8 (2.8)
LS Mean Change ^e	-8 (2.7)	-10 (2.7)	5 (5.6)	-12 (2.6)	-11 (3.3)
MAP (mm Hg)					
n	27	26	5	26	21
Baseline	97 (1.9)	97 (1.5)	95 (8.6)	96 (1.7)	94 (1.8)
Week 8 ^d	89 (1.5)	90 (1.8)	94 (13.4)	88 (2.0)	87 (1.9)
Mean Change	-8 (1.8)	-7 (1.6)	-1 (5.1)	-8 (1.8)	-7 (2.0)
LS Mean Change ^e	-9 (1.9)	-9 (1.9)	0 (4.0)	-9 (1.9)	-10 (2.3)

No meaningful differences between all school age and adolescent categories could be discerned with regard to their respective mean changes from baseline in DBP, SBP, and MAP at Week 8.

Assessor's comment: In the analysis performed on the DBP, SBP, and MAP at 2 and 8 weeks, there appeared to be a difference between the quinapril 5-mg dose group and each of the other active treatment groups (2.5, 10, and 20 mg quinapril groups). The applicant argues that, this may be due to inadequate patient designation to 5mg dose group (n = 5). The applicant further claims that "A post hoc analysis, involving the removal of only 1 possibly discrepant patient with clinically paradoxical data from the 5 mg treatment group, demonstrated that these dose versus dose comparisons became nonsignificant".

Change From Baseline in DBP& SBP at Weeks 2 and 8 by Milligram per Kilogram Dose

At Weeks 2 and 8 the analysis of the response for both SBP and DBP on a milligram per kilogram basis did not show a statistically significant relationship between the magnitude of the blood pressure response and dose normalized by patient weight. Regression of Milligram per Kilogram on Change from Baseline in DBP were (Wk2, Slope, P = 0.6551) and (Wk 8, Slope, P = 0.7026) and in SBP were (Wk2, Slope, P = 0.1282) and (Wk 8, Slope, P = 0.7601).

Percent of Responders after 2 & 8 Weeks of Treatment (All Patients)

Responders were defined as patients who demonstrated a ≥ 10 mm Hg drop in SBP or ≥ 5 mm Hg drop in DBP or reduction of SBP and DBP to < 90 th percentile for gender, age, and height. The analysis was performed at Weeks 2 and 8. The results of evaluation of the percent of

responders of all patients who had received active treatment are summarised in the tables (10 & 11) below:

Table 10- Week 2 Percent of Responders and Non Responders, All Patients [N (%)]

	Placebo ^c	Quinapril mg QD				All Doses ^d
	N = 27	2.5 N = 29	5 N = 5	10 N = 27	20 N = 24	
n ^e	27	27	5	26	23	81
Responders	17 (63.0)	17 (63.0)	2 (40.0)	14 (53.8)	19 (82.6)	52 (64.2)
Non Responders	10 (37.0)	10 (37.0)	3 (60.0)	12 (46.2)	4 (17.4)	29 (35.8)

Table 11- Week 8 Percent of Responders and Non Responders, All Patients N (%)

	Quinapril 10 mg QD ^c for 6 weeks N = 27	Quinapril mg QD				All Doses ^e N = 85
		2.5 N = 29	5 N = 5	10 ^d N = 27	20 N = 24	
Week 8 n ^f	27	26	5	26	21	78
Responders	21 (77.8)	18 (69.2)	3 (60.0)	22 (84.6)	15 (71.4)	58 (74.4)
Non Responders	6 (22.2)	8 (30.8)	2 (40.0)	4 (15.4)	6 (28.6)	20 (25.6)

Using logistic regression there was no significant difference in responder rate at 2 weeks ($p = 0.16$) or 8 Weeks ($p = 0.80$) among the treatment groups.

Assessor's comment: there seems to be no differences in percentage of the responders in all treatment doses compared to the placebo group, in either 2 or 8 weeks treatment durations.

Percent of Patients with Reduction of DPB & SBP to <90th Percentile for Gender, Age, and Height at Weeks 2 and 8

Results of the evaluation of the percent of patients with reduction of SBP and DBP to <90th percentile for gender, age, and height after 2 and 8 weeks of treatment, are summarized in the tables (12 & 13) below:

Table 12- Week 2 Percent of Patients with Reduction of DPB & SBP to <90th Percentile for Gender, Age, and Height [N (%)]

	Placebo	Quinapril mg QD				All Doses ^a
	N = 27	2.5 N = 29	5 N = 5	10 N = 27	20 N = 24	
Patients With Reduction <90 th Percentile	3 (11.1)	8 (27.6)	1 (20.0)	5 (18.5)	10 (41.7)	24 (28.2)

Table 13- Week 8

	Quinapril 10 mg QD ^a for 6 Weeks N = 27	Quinapril mg QD				All Doses ^c N = 85
		2.5 N = 29	5 N = 5	10 ^b N = 27	20 N = 24	
Patients With Reduction <90 th Percentile	10 (37.0)	5 (17.2)	1 (20.0)	12 (44.4)	7 (29.2)	25 (29.4)

In the evaluation of patients with reduction of SBP and DBP to less than the 90th percentile for gender, age, and height and Weeks 2 and 8, no inferential analysis was performed and no meaningful differences among the treatment groups could be discerned.

Assessor's comment: analysis of percentage of patients with reduction of SBP and DBP to below the 90 percentile for gender, age, and height after 2 & 8 weeks of treatment, in all doses of quinapril, seems to be nearly 3 folds higher than in placebo. This trend is seen in both SBP & DBP for 2 and 8 weeks treatment durations. The logistic regression for this was not provided by the applicant. This pattern is repeated in patients that were crossed over from placebo to 10 mg, where after 6 weeks the percentage of responders is 37% nearly 3 fold of the placebo 11%.

Only 6 patients (5.4%) initiated therapy with or increased their dose of HCTZ during the study (1 Adolescent and 5 School Age patients). No meaningful difference could be discerned between treatment group and initiation or dose increase of HCTZ.

Analysis within Weight Strata DBP and SBP at Week 2

Stratum A: patients weighing 20 to 40 kg who had received active treatment (2.5, 5, and 10 mg quinapril) once daily had adjusted least square mean changes in DBP of -7, -1, and -8 mm Hg, respectively, compared with -19 mm for the placebo group; and for SBP -12, -2, and -3 mm Hg, respectively, compared with -8 mm Hg for the placebo group. There were no statistically significant linear dose responses for DBP and SBP across the treatment groups ($p = 0.2378$ and 0.3263 , respectively).

Stratum B: patients weighing >40 kg who had received active treatment (2.5, 10, and 20 mg quinapril) once daily had adjusted least square mean changes in DBP of -2, -3, and -6 mm Hg, respectively, compared with -3 mm Hg for the placebo group; and for SBP -7, -5, and -7 mm Hg, respectively, compared with 0 mm Hg for the placebo group. There were no statistically significant linear dose responses for DBP or SBP across the treatment groups ($p = 0.2010$ and 0.0667 , respectively).

Efficacy Summary

- DBP: at Week 2 for both the evaluable and all patient populations there were no statistically significant dose responses across the dose groups for DBP ($p = 0.06$ and $p = 0.10$, respectively).

- SBP: at Week 2 for all patients, there was a statistically significant linear dose response across treatments ($p = 0.02$) with a significant difference between the quinapril 20 mg QD and placebo treatment groups ($p = 0.02$). In patients who were ≥ 90 th percentile for SBP at baseline, there was a statistically significant dose response across the treatment groups ($p = 0.01$), with a significant difference between the quinapril 20 mg QD and placebo treatment groups ($p = 0.02$).

- MAP: at Week 2 for all patients, there was a significant linear dose response across the treatments for all patients ($p = 0.03$), however, there were no statistically significant differences between placebo and any individual dose.

- Dose versus dose comparisons: all patients DBP, SBP, and MAP responses at Week 2 and 8, although there appeared to be statistically significant dose versus dose comparisons these were all between the quinapril 5 mg treatment group (which contained only 5 patients) and other active treatment groups. A post hoc analysis, involving the removal of only 1

possibly discrepant patient with clinically paradoxical data from the 5 mg treatment group, demonstrated that these dose versus dose comparisons became nonsignificant.

- Milligram per kilogram analysis: on the response for all patients there were no statistically significant effects from regression analyses for the change from baseline in DBP and SBP and Weeks 2 and 8.

- Responders / Non Responders analysis: at Weeks 2 and 8 for all patients, no significant differences in responder rates for the treatment groups were demonstrated. No inferential analysis was performed in the evaluation of patients with reduction of SBP and DBP to less than the 90th percentile for gender, age, and height and Weeks 2 and 8.

- Few patients needed the addition or dose increase of HCTZ in addition to quinapril for control of blood pressure. There were no withdrawals due to lack of efficacy or adverse events.

- For all patients no meaningful difference could be discerned between school age and adolescent populations.

- **Pharmacokinetic results** – Not previously assessed

Patients were divided in to 5 Groups; 1: placebo, 2: 2.5 mg, 3: 5mg, 4: 10 mg and group 5: 20 mg. Samples from 38 patients were analyzed in the pharmacokinetic portion of the study. Body weight varied widely in patients ranging from 26.4 to 161.2 kg. With the exception of 5 patients (Group 3) and 2 patients (Group 1), all patients were from Stratum B (>40 kg).

Mean plasma quinaprilat concentration-time profiles are depicted in figure 4 below for each treatment group. Quinaprilat pharmacokinetic parameter values are summarized with patient demographic data in table 14.

Figure 4- Mean Quinaprilat Plasma Concentrations vs. Time by Treatment Group:

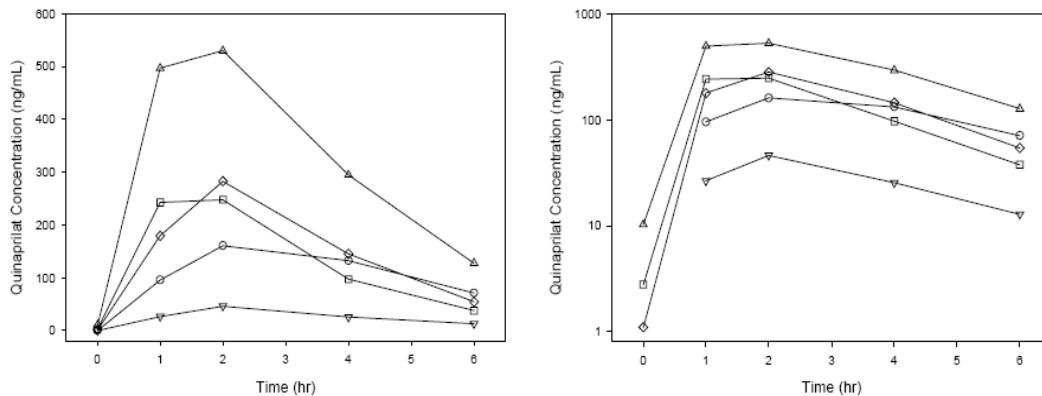


Table 14- Quinaprilat PK Parameter Values (Mean \pm SD) by Treatment Group

Parameter	Treatment Group				
	1	2	3	4	5
n	12	7	3	5	11
Dose (mg QD)	Placebo/10	2.5	5	10	20
Dose (mg/kg)	0.161 ± 0.093	0.030 ± 0.016	0.165 ± 0.020	0.131 ± 0.056	0.293 ± 0.106
Age (years)	13.0 ± 2.4	13.6 ± 1.7	7.3 ± 2.1	11.2 ± 2.8	12.8 ± 2.2
Weight (kg)	75.8 ± 28.2	105.4 ± 48.1	30.5 ± 3.4	90.1 ± 42.1	76.4 ± 26.2
BSA (m ²)	1.76 ± 0.40	2.07 ± 0.51	1.02 ± 0.05	1.86 ± 0.47	1.78 ± 0.36
CLcr (mL/min)	96.3 ± 31.1	124.3 ± 46.5	52.7 ± 2.5	113.8 ± 41.9	97.4 ± 23.7
nCLcr (mL/min/1.73m ²)	92.4 ± 15.4	103.0 ± 23.4	89.8 ± 1.9	103.9 ± 15.5	94.5 ± 12.5
Cmax (ng/mL)	219 ± 118	46.2 ± 24.4	285 ± 27.5	304 ± 172	714 ± 437
tmax (hr)	2.2 ± 1.2	2.3 ± 0.8	1.7 ± 0.6	2.4 ± 0.9	2.0 ± 1.1
AUC(0-tlqc) (ng·hr/mL)	672 ± 375	160 ± 81.4	863 ± 118	921 ± 485	2017 ± 873
t½ (hr)	1.73 ± 0.37 ^a	1.92 ± 0.25 ^a	1.42 ± 0.08	1.54 ± 0.33	1.67 ± 0.38

^a t½ determined in 9/12 patients in Group 1 and 6/7 patients in Group 2.

AUC and Cmax values of quinaprilat increased linearly with increasing dose on a mg/kg basis. The quinapril dose ranged from 0.016 to 0.468 mg/kg. The relationships were described using a linear regression analysis.

Individual quinaprilat exposure range was 1764 ng/mL for Cmax and 3647 ng·hr/mL for AUC. Thus, the highest level of exposure observed in these paediatric patients was similar to the average Cmax (1760 ng/mL) and AUC (3350 ng·hr/mL) at doses of 80 and 40 mg, respectively, in adults.

Quinaprilat Cmax and AUC were normalized to a 0.2 mg/kg dose and examined as a function of age. A trend of increasing exposure was noted over the age range (5-16 years) although there was considerable overlap in individual Cmax and AUC values. Summary statistics are provided in table 15 for adolescent and school age patients.

Table 15- Quinaprilat Pharmacokinetic Parameter Values and Demographics

Parameter	School Age	Adolescent
n	22	16
Dose (mg/kg) ^a	0.203 ± 0.134 (0.018-0.468)	0.128 ± 0.085 (0.016-0.294)
Age (year)	11.1 ± 2.6 (5-15)	14.1 ± 1.8 (11-16)
Weight (kg)	66.2 ± 35.0 (26.4-156)	98.4 ± 30.6 (63.6-161)
Cmax (ng/mL) ^b	316 ± 142 (0-658)	479 ± 188 (278-885)
AUC(ng·hr/mL) ^b	996 ± 418 (0-1986)	1430 ± 531 (710-2608)

^a Actual dose administered

^b Cmax and AUC normalized to a 0.2-mg/kg dose

When normalizing to a 0.2 mg/kg quinapril dose, Cmax and AUC values for quinaprilat was 30-34% lower in school age children relative to adolescents. This difference may be due to the non-linear relationship between weight and body surface area. Overall mean ± SD Cmax and AUC were 384 ± 180 ng/mL and 1179 ± 510 ng·hr/mL, respectively.

Pharmacokinetic Summary

Quinapril was absorbed and converted rapidly to quinaprilat with measurable quinapril plasma concentrations generally observed only in samples collected at 1 and/or 2 hours post-dose. Quinaprilat pharmacokinetic parameters (AUC and Cmax) in 38 paediatric patients increased linearly with quinapril dose, which ranged from 0.016 to 0.468 mg/kg. Overall, individual quinaprilat exposure ranged up to 1764 ng/mL and 3647 ng·hr/mL for Cmax and AUC, respectively. Thus, the highest Cmax value observed in these paediatric patients was similar to the average Cmax (1760 ng/mL) observed at a dose of 80 mg in adults. When normalizing to a

0.2 mg/kg quinapril dose, a trend of increasing exposure was noted over the age range (5-16 years) although there was considerable overlap in individual Cmax and AUC values.

Assessor's comment: as quinapril is rapidly metabolised to its active metabolite, quinaprilat, the MAH has measured the latter, which is appropriate. The sample collection times for measuring quinaprilat PK values are acceptable.

The 38 patients included in the PK study had an average age of 11 - 14 weighing 66-98 kg on average. How indicative of paediatric population this is?

The average half life of quinaprilat in paediatric population tested is 1.7 to 2.4 hrs, which is similar to that of the adults 2 hrs.

AUC and Cmax values of quinaprilat increased linearly with increasing dose of quinapril when expressed on a mg/kg basis.

The highest Cmax value observed in these paediatric patients (1764 ng/mL) was similar to the average Cmax (1760 ng/mL) observed at a dose of 80 mg in adults.

The highest AUC value observed in these paediatric patients (3647 ng·hr/mL) was similar to the average Cmax AUC (3350 ng·hr/mL) observed at a dose of 40 mg in adults.

Normalized to a 0.2 mg/kg quinapril dose, a trend of increasing exposure was reported over the age range (5-16 years) although there was considerable overlap in individual Cmax and AUC values.

A short description of these data should be included in the 5.2 of the SPC.

- **Safety results**

Extent of Exposure

For patients randomized to active treatment, the mean number of days that patients were on study medication was similar among dose groups (range 51 to 55 days). Patients were on placebo for a mean of 15 days followed by quinapril 10 mg QD for a mean of 42 days.

Overall, 57 of 112 (51%) patients experienced treatment-emergent adverse events. Thirteen (11.6%) patients had adverse events associated with the treatment. There was a greater percentage of school age patients with associated adverse events (15%) compared with adolescent patients (8%). A similar percentage of girls and boys experienced treatment-associated AEs (boys 11%; girls 13%). The percentages of patients with AEs were similar among the 3 races (white 15%; black 13%; and Hispanic 10%). All adverse events were mild or moderate in intensity; with 42 of 112 (38%) mild and 15 of 112 (13%) moderate adverse event.

Associated Adverse Events

A line listing of associated adverse events are presented in Table 16 below. Nine school age and 4 adolescent patients experienced treatment-related adverse events. All associated adverse events occurred while patients were on active treatment. Associated adverse events reported by more than one patient included dizziness (3 patients), headache (3 patients), and acidosis (decreased bicarbonate), asthenia, and tachycardia (2 patients each).

Table 16- Listing of Patients with Associated Adverse Events

School Age/ Adolescent	Patient Number	Treatment Group	Adverse Event	Intensity
School Age	2-2010	10 mg quinapril	Dizziness Hypotension	Mild Mild
School Age	7-7003	10 mg quinapril	Nervousness	Mild
School Age	9-9003	10 mg quinapril	Acidosis	Mild
School Age	13-13011	10 mg quinapril	Tachycardia	Mild
School Age	13-13012	20 mg quinapril	Asthenia Headache	Mild Mild
School Age	13-13022	10 mg quinapril	Cough increased	Mild
School Age	13-13023	20 mg quinapril	Tachycardia Asthenia	Mild Mild
School Age	17-17006	10 mg quinapril	Dysuria Headache	Moderate Moderate
School Age	105-105003	10 mg placebo/quinapril QD ^a	Dizziness	Mild
Adolescent	9-9002	10 mg quinapril	Acidosis Hypochloremia	Mild Mild
Adolescent	13-13008	20 mg quinapril	Abdominal pain	Mild
Adolescent	13-13030	10 mg placebo/quinapril QD ^a	Syncope Dizziness Headache	Mild Mild Mild
Adolescent	26-26002	10 mg placebo/quinapril QD ^a	Leukopenia	Moderate

The most frequently reported adverse events by preferred term were infection (13%), headache (13%), pharyngitis (13%), rhinitis (10%), and increased cough (10%).

All treatment-related adverse events were assessed by the investigator as mild with the exception of 3 events: 1 school age patient had dysuria and headache, both assessed as moderate in intensity; 1 adolescent patient had leukopenia assessed as moderate.

The AEs reported in this study, have also been observed in adults (specifically in 0.5% or more of adults participating in randomized placebo-controlled quinapril hypertension trials. These treatment-related adverse events were: Dizziness and headache (3 patients, each); asthenia and tachycardia (2 patients, each); and increased cough, nervousness, and abdominal pain (1 patient, each). There were no serious adverse events, deaths, or withdrawals due to adverse events.

Laboratory Values

There was a shift from normal to below normal serum bicarbonate values in 21 patients (19 patients on quinapril treatment, 2 patients 47 and 105 days post-treatment). Thirteen of the 19 patients had normal anion gap and 6 patients had high anion gap. None of the normal anion gap-type patients appeared to have Type IV hyperkalemic renal tubular acidosis (RTA), which can be associated with ACE inhibition. While it is not possible to determine a clearly identifiable cause in all of the patients with low serum bicarbonate, there were several factors that may have contributed to the decrease in some patients.

Factors include underlying disease (renal disease, diabetes), background medication (HCTZ), and problems inherent in generating accurate measures of serum bicarbonate. Of the 19 (18.4%) treated patients who had decreases in bicarbonate, 4 had small decreases (ie, 1-2 mEq/L), 6 patients had laboratory collection and handling problems known to result in

measurement errors, and 7 patients had underlying disease and/or were on background medications that may cause a decrease in bicarbonates. Two patients had low serum bicarbonate reported as an adverse event. These bicarbonate changes were consistent with shifts from normal to below normal seen previously in adult populations in quinapril studies and were reported in 9% of patients (108 of 1179 patients) for quinapril studies of hypertension (1988).

Assessor's comment: The bicarbonate changes below normal observed in this study may be consistent with that of quinapril adult studies, but the frequency of it in children is doubled. Whilst 9% adults had low bicarbonate serum level, nearly twice as many children (19%) in this study had experienced low bicarbonate levels. The applicant needs to discuss frequency and perhaps severity in adults vs. children.

In addition it was noted that 9 patients had hematuria at their final evaluation. Eight were menarchal females and 1 was male. Information regarding last known menstrual period was not collected, but given that all 8 cases of hematuria in females occurred in those who were menarchal, it seems likely that hematuria in these patients may have been related to menses. The male had a history of kidney disease.

Discussion on clinical aspects

Efficacy Discussion

The efficacy study in this submission has failed to reach its primary objective of reduction of DBP after 2 weeks. There are a number of reasons for this failure, chiefly the enrolment of patients with elevated SBP but normotensive DBP in the attempt to recruit more patients. The neutral result for DBP may also have been influenced by the relatively high body weight of the study population. Interpretation of DBP results is further complicated by a high mean DBP placebo response, particularly in the school age patients. Despite the lack of statistical significance for the primary analysis, analyses of secondary parameters demonstrated the efficacy of quinapril in reducing SBP at 2 weeks and a significant dose response relationship. Furthermore a clear 3 fold higher percentage of responders in patients with reduction in both SBP and DBP at 2 and 8 weeks compared with placebo, were observed.

It is important that the current results are discussed in the context of available information on quinapril. Unfortunately the review of the published literature, provided by the applicant is deficient of any information. The extend of quinapril use in children is not known and independent evidence for beneficial effects in controlling blood pressure in paediatric population is also unknown.

In summary, the primary efficacy end point of reduction in diastolic blood pressure was not reached, nor was a dose – response slope for DPB established. Although quinapril was efficacious in reducing Systolic blood pressure in the population studied, the evidence is not robust enough to justify paediatric indication. This conclusion is in line with the earlier outcomes of the UK assessment in December 2004 and FDA in September 2002 that reviewed the efficacy results of the current study. Further recommendations for harmonised wording of the summaries of product characteristics for other ACE inhibitors, were made:

Section 4.2

Children and adolescents

There is limited clinical trial experience of the use of Quinapril in hypertensive children aged 5 years and above. There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.

Section 5.1

In a randomised clinical trial using target doses of 2.5, 5 , 10 and 20mg of quinapril, 112 children and adolescents with hypertension or high normal blood pressure over 8 weeks (2 weeks double blind and 6 weeks extension), a reduction in systolic blood pressure alone was noted across all treatment groups. The reduction in diastolic pressure overall, and for each group was similar to placebo in this group of subjects suggesting that a dose response effect was not established.

Pharmacokinetics discussion

Study 906-434

Quinaprilat exposure in infants and children is similar across the age range of 2.5 to 82 months when quinapril is dosed on a milligram per kilogram basis. Exposure following a single 0.2-mg/kg dose is comparable to that observed in adults after a single 10-mg dose. CL_{cr} is a good predictor of quinaprilat oral clearance.

Study 906-427/440

Quinaprilat pharmacokinetic parameters (AUC and C_{max}) in 38 paediatric patients increased linearly with quinapril dose which ranged from 0.016 to 0.468 mg/kg. Overall, individual quinaprilat exposure ranged up to 1764 ng/mL and 3647 ng·hr/mL for C_{max} and AUC, respectively. Thus, the highest C_{max} value observed in these paediatric patients was similar to the average C_{max} (1760 ng/mL) observed at a dose of 80 mg in adults. However the text of the section 5.2 proposed by the applicant has not included any of the results of the multiple dose PK study 906-427/440.

Safety Discussion

Study 906-434

No particular concerns were found from this single dose study on the 24 patient's who were already on other ACE inhibitors.

Study 906-427/440

The safety profile for quinapril 2.5 to 20 mg in paediatric patients ages 5 to 16 with hypertension is similar to that seen in adult patients. Treatment-related adverse events that occurred in this study that have also been observed in adults (in 0.5% or more of adults participating in randomized placebo-controlled quinapril hypertension trials) were dizziness and headache (3 patients each); asthenia and tachycardia (2 patients, each); and increased cough, nervousness, and abdominal pain (1 patient).

All adverse events in this study were mild or moderate in intensity. There were no severe or serious adverse events, no withdrawals due to adverse events, and no deaths. There were no apparent changes in physical findings or in vital signs, including changes in heart rate or body weight. In most instances laboratory values remained within normal ranges throughout the study. No patients withdrew due to, adverse events or serious adverse events.

RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION (PRELIMINARY)

➤ Overall conclusion

The efficacy study in this submission has failed to reach its primary objective of reduction of DBP after 2 weeks. There are a number of reasons for this failure, chiefly the enrolment of patients with normotensive DBP in the attempt to recruit more patients. Although quinapril demonstrated some efficacy in reducing SBP this evidence is by no means robust enough for paediatric indication.

Quinaprilat AUC and Cmax increased linearly with quinapril dose in the paediatric population tested. Overall, pharmacokinetics of quinapril in children were consistent with pharmacokinetics of quinapril in adults. However the text of the section 5.2 proposed by the applicant does not include the results of the multiple dose PK study 906-427/440 and needs major alterations.

The safety profile of quinapril generally resembles that of adults and no new AE or pattern of incidences in children has emerged with exception of doubled frequency of low bicarbonate in children compared to adults that needs to be addressed by the MAH. Otherwise no change to section 4.8 is required.

➤ **Recommendation** (Preliminary)

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy, taking into account the previous national assessment in the UK in Dec 2004, the Rapporteur considers that the results of these studies do not support a paediatric posology. However, the incorporation of summaries of efficacy and PK findings in section 5.1, 5.2 and a cross reference in section 4.2 of the SmPC will be helpful to the prescriber.

The safety profile of quinapril generally resembles that of adults and no new adverse event (AE) or pattern of incidences in children has emerged as a result of the submitted data. No change to section 4.8 is required.

The following changes to the SmPC are recommended (in italics and strike through). The Rapporteur agrees with the applicant's proposed text for Sections 4.2 and 5.1 (as is in the existing UK SmPC):

4.2 Posology and method of administration

Paediatric population

Quinapril is not recommended for use in children and adolescents due to insufficient safety and efficacy data. There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above (See section 5.1& 5.2). There are no data regarding children below 5 years of age.

5.1 Pharmacodynamic properties

In a randomised 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), a reduction in systolic blood pressure alone was noted across all treatment groups at the end of 2 weeks only. A dose response effect between groups was not seen. The reduction in diastolic pressure overall, and for each group was similar to placebo in these subjects suggesting that a dose response effect was not established. Long term effects of quinapril on growth, puberty and general development have not been studied.

The text of the section 5.2 proposed by the applicant has not included the results of the multiple dose PK study 906-427/440, therefore the Rapporteur proposes the following text for section 5.2:

The pharmacokinetics of quinapril has been studied in a single dose (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.

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 2.30 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 C_{max} values of quinaprilat were observed to increase linearly with increasing dose of quinapril on a mg/kg basis.

REQUEST FOR SUPPLEMENTARY INFORMATION

Study 906-427/440; the applicant needs to address the following:

- 1- The bicarbonate changes below normal observed in this study may be consistent with that of quinapril adult studies, but the frequency of it in children is nearly doubled. The applicant needs to discuss frequency and perhaps severity in adults vs. children.
- 2- The proposed text of the section 5.2 should include the results of the multiple dose PK data.

ASSESSMENT OF THE COMPANY RESPONSE

Following the circulation of the preliminary assessment report (pages 6 – 31) on 20 January 2010, and subsequent CMS comments, a list of comments and questions was sent to the applicant. The applicant's response including a further literature search and proposed changes to the SmPC text were received on 17 May 2010. The assessment of this response is detailed below:

Comment 1.

Assessor's comment: the review of the published literature, provided by the applicant is deficient of any information and fails to identify published articles and abstracts that are relevant to quinapril in a paediatric population.

Response: In the initial submission dated of August 2009, the literature was reviewed as follows:

"For a review of the published literature, MEDLINE, EMBASE, BIOSIS, and Derwent Drug File were manually searched through 17 August 2009 for all clinical trials, case reports, and epidemiology studies with the following terms: quinapril OR accupril OR 85441-61-8.RN AND hypertension OR high ADJ blood ADJ pressure OR HTN OR HPN AND (adolescent OR adolescence OR '17' ADJ years OR under ADJ '18') AND (pediatric OR pediatrics OR paediatric

OR paediatrics OR child OR children). The individual publications were then reviewed for relevance. An important caveat of the literature review is that it reflects current information available in the public domain, which may not reflect the totality of the data since not all reports are published. One published report of children treated with quinapril was identified. Blumer et al(3) , a dedicated pharmacokinetic study was conducted in pediatric patients chronically maintained on ACE inhibitors, other than quinapril, rather than healthy infants and children.”

Based on the above comment 1, a second search was performed to capture a broader range of relevant available literature. MEDLINE, EMBASE, BIOSIS, and Derwent Drug File were manually searched through 24 April 2010 for all literature containing the following terms/criteria: quinapril OR accupril OR 85441-61-8.RN AND child OR children OR pediatric OR paediatrics OR childs OR kid OR kids OR paediatric OR paediatrics OR toddler OR toddlers OR adolescent OR adolescents OR infant OR infants OR juvenile OR juveniles.

A review of the literature captured from this query did not reveal any additional relevant findings for the use of quinapril in a pediatric population. Therefore, the only primary publication which was found to be specific to quinapril in a paediatric population is the Blumer et al paper which was identified during the initial submission. This publication has also been reviewed and discussed in the Clinical Overview dated of 20 August 2009. No further publication specific to quinapril has been identified during the second literature search.

<p>Assessor’s comment: The applicant has carried out a second literature search with broader range of relevant available literature and has stated that no further new publication were resulted from the second search. ISSUE RESOLVED.</p>
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Comment 5, Study 906-427/440:

Assessor’s comment: 93% of randomized patients had SBP that was greater than or equal to the 90th percentile, but nearly half of all randomized patients had DBP that was less than 90th percentile for gender, age and height at baseline. This makes the whole study futile and meaningless as the primary objective of reduction in DBP is tested in a population where almost half of them do not have raised DBP at the baseline. The applicant needs to justify the recruitment of patients with normal DBP for a study with primary objective of lowering DBP.

Further more 78% of patients had essential hypertension and only 22% of patients had secondary hypertension; as school age children are usually prone to secondary hypertension, this limits the clinical usefulness of the study.

Response: Clinical study 906-427/440 was designed with input from the US Food and Drug Administration (FDA) through a Written Request to investigate the safety and efficacy, including dose response, of quinapril in the treatment of children between 5 and 16 years of age who had mild to moderate hypertension. The inclusion criteria included subjects with a diagnosis of hypertension defined as SBP and/or DBP ≥90th percentile for age, gender, and height.

DBP was chosen as the primary efficacy parameter because change in DBP at trough was the endpoint of choice for FDA regulatory submissions for hypertension when the study protocol was written. The inclusion criteria did not require all subjects to have an elevated DBP. In retrospect, the greater variability of DBP compared with SBP in young children suggests that SBP might have been a more suitable primary efficacy parameter. In addition, more recent observations

suggest that systolic hypertension is more common than diastolic hypertension in pediatric patients. Indeed, systolic hypertensives outnumbered diastolic hypertensives in Study 906-427/440. In the pediatric study population, 93% of randomized patients had SBP that was greater than or equal to the 90th percentile, but nearly half of all randomized patients had DBP that was less than 90th percentile for gender, age, and height at baseline. Inclusion of patients with BP \geq 90th percentile was selected rather than 95th percentile with the FDA's concurrence, because the use of placebo was raised as an ethical concern by experts and by the FDA in the Written Request. Inclusion of milder hypertensive patients seemed prudent for a dose ranging trial in which patients could be randomized either to placebo or to a drug not tested previously in children. However, the relatively high proportion of patients with DBP $<$ 90th percentile may have influenced the neutral result for change in DBP, since the effect of quinapril is minimal in normotensive patients. Quinapril studies in adults have demonstrated that quinapril lowers BP only slightly in normotensive patients and that there is a correlation between severity of baseline hypertension and BP response to quinapril.

In summary, this study was designed to be responsive to the FDA's Written Request.

Results indicate that quinapril had a significant dose-related effect on SBP compared with placebo, but efficacy was not demonstrated for DBP. The neutral result for DBP may have been influenced by the unexpectedly high proportion of high body weight and low baseline DBP in these pediatric patients. Interpretation of DBP results is further complicated by a high mean DBP placebo response, particularly in the School Age patients. In retrospect, SBP might have been a better choice for primary efficacy parameter, because of the prevalence of systolic hypertension in children and because SBP can be measured more accurately than DBP in younger children.

Assessor's comment: recently, a pattern of failed paediatric antihypertensive trials has emerged; this led in turn to analysis of 6 paediatric anti-hypertensive studies during 1998 - 2005 (Benjamin et al 2008). The results of this analysis support the use of reduction in sitting diastolic blood pressure as the primary end point, as it has less physiological variability among observations within a subject than systolic blood pressure in children.

The choice of reduction in diastolic blood pressure as primary efficacy parameter in this study is not disputed. It is the inclusion criteria and/or recruiting policy of a population where almost half of the children did not have raised DBP at the baseline; that has possibly led to the failure in demonstrating efficacy. Systolic hypertension is approximately 3-fold more common than diastolic hypertension (Sorof 2001) and the motivation to recruit patients with elevated systolic blood pressure derives from feasibility, a common problem in conducting paediatric trials.

None the less the applicant's original decision to recruit children with elevated systolic BP may not have been astute but was within the guidelines at the time and can not be scrutinized at this point. **ISSUE RESOLVED.**

Comment 11. Study 906-427/440:

The 38 patients included in the PK study had an average age of 11 - 14 weighing 66-98 kg on average. How indicative of paediatric population this is?

Response: The most frequent etiology of hypertension in all dose groups studied in the efficacy and safety portion of the trial was primary or essential hypertension (overall range 60.0% to 89.7 of patients), and its occurrence was similar in School Age and Adolescent populations. The

frequency of essential hypertension among School Age children in the study was unexpectedly high. It has been reported that the majority of children and adolescents with mild to moderate hypertension have primary hypertension in which a cause is not identifiable. Hypertension in children has been shown to correlate with family history of hypertension, low birth weight, and excess weight. One report estimated the number of children with obesity-related disease risk factors and co-morbidities, including hypertension in the European Union.

The study reported over a million obese children are likely to have a range of cardiovascular disease indicators in the EU, with an estimated 1.1 million suffering hypertension. It has also been estimated that by year 2010 the European Union can expect to see the numbers of overweight and obese children rising by approximately 1.3 million children per year, of which the numbers of obese children would be rising by over 0.3 million per year.

Overall, the high frequency of essential hypertension in the trial and an unexpectedly high body weight distribution suggest that a large number of patients in the trial may have had hypertension associated with obesity. Patient weights were distributed disproportionately to the > 40 kg stratum in both the efficacy study and in the subset of patients in the PK study.

Many of the weights were much larger than expected based upon weight tables for gender, age, and height. For the subset of patients in the PK study, body weight varied widely ranging from 26.4 to 161.2 kg. With the exception of 5 patients (Group 3) and 2 patients (Group 1), all patients were from Stratum B (> 40 kg).

Given the high body weight distribution, suggestive of hypertension associated with obesity, in the overall study and subsequent subset of patients in the PK study, and the reported increased prevalence of obesity and hypertension in School Age as well as the Adolescent population, the MAH is of the opinion that the patient population studied is indicative of pediatric patients with hypertension.

Assessor's comment: as the applicant stated in the response "...the high frequency of essential hypertension in the trial and an unexpectedly high body weight distribution suggest that a large number of patients in the trial may have had hypertension associated with obesity. Patient weights were distributed disproportionately to the > 40 kg stratum in both the efficacy study and in the subset of patients in the PK study". The assessor is of the opinion that this information is important and may influence the prescribers and therefore should be captured in the section 5.2 **ISSUE RESOLVED**.

All the other assessor's comments were accepted by the applicant.

Question 1, Comment 12. Study 906-427/440:

The bicarbonate changes below normal observed in this study may be consistent with that of quinapril adult studies, but the frequency of it in children is nearly doubled. The applicant needs to discuss frequency and perhaps severity in adults vs. children.

Response: The review of carbon dioxide and bicarbonate changes observed in the adult Integrated Summary of Safety Information for quinapril and paediatric study: An 8-Week, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Safety and Efficacy of Quinapril in Paediatric Patients With Hypertension (QUIK) (Protocol 906-427/440) shows that the rates of bicarbonate declining at least 4 mEq/L are consistent between adults and children and between children not on and on quinapril treatment. The safety profile for quinapril administered to paediatric patients in QUIK was similar to that in adult patients.

Pfizer proposes that the data show the frequency of decrease of bicarbonate by least 4 mEq/L is virtually indistinguishable between the studied adults and children and the children not on treatment and those on quinapril, therefore, recommendations for specific paediatric monitoring and comparative frequency tables are not necessary. Thus, the MAH is not proposing any changes to Section 4.4. Acidosis was not supported by an increase in hydrogen ion concentration (low pH), but the reduction in bicarbonate levels is supported by the laboratory assessments conducted. Therefore, the MAH recommends adding the term "Blood bicarbonate decreased" as a paediatric specific adverse event in section 4.8 of the SmPC, with a frequency of "Common" (1/100 to <1/10) and to update the corresponding PIL accordingly.

Assessor's comment: The applicant carried out a review of Integrated Summary of Safety Information for quinapril HCL tablets in adult (RR-X-720-02504, n=2697) and the safety information from the current paediatric study (906-427/440, n=103), taking in to account different AE terminology and measurement methods of bicarbonate or carbon dioxide and found that the proportion of adult and paediatric patients who experience a bicarbonate decline of at least 4 mEq/L appears to be comparable. Likewise, the proportion appears to be comparable between paediatric patients on quinapril and those who were not.

There seem to be only 2 cases of mild acidosis in the children with bicarbonate of 2 mEq/L below normal. On one which was confounded by type 1 diabetes mellitus and had values consistent with ketoacidosis.

It seems that the frequency or severity of adverse event of low bicarbonate, carbon dioxide or acidosis in children, is not particularly alarming and there is no need for inclusion of these findings in the 4.8 of the SmPC. **ISSUE RESOLVED.**

Question 2, Study 906-427/440;

The proposed text of the section 5.2 should include the results of the multiple dose PK data.

Response: Pfizer agrees to include the results of the multiple dose PK study 906-427/440 in Section 5.2 as follows:

"Section 5.2:

*The pharmacokinetics of quinapril has been studied in a single dose (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 C_{max} values of quinaprilat were observed to increase linearly with increasing dose of quinapril on a mg/kg basis."

Assessor's comment: Applicants insertion of "**weighing 66-98 kg on average**" in to the proposed Rapporteur's text of section 5.2 of the SmPC is acceptable. **ISSUE**

RESOLVED.

Day 85 Comments And Questions Received From The Other MSs,

A few concerned members of state have commented on this procedure, on the whole they all endorsed the Rapporteur's conclusion that the submitted data do not support a paediatric posology and also agreed to the Rapporteur's proposal for sections 4.2. and 5.2.

With regard to section 5.1, the opinion is divided. One member state do not support the inclusion of information in section 5.1 of the SPC, because this information may be misleading. They argue that in fact, a clinical effect of quinapril in the paediatric population should have been expected had the correct population been recruited.

Another member of state agrees to include the results of these studies in section 5.1 and further suggested providing the prescribers with a more accurate view of the negative results of the performed study.

Assessor's comment: If the design or recruitment of the current paediatric studies were ideal, and the efficacy of quinapril in achieving the primary objective of reducing diastolic blood pressure was clearly and unequivocally demonstrated, a paediatric indication would be permissible in the sections 4.1 and/or 4.2 of the SmPC. However the primary objective was not achieved, but quinapril produced statistically significant reduction of systolic blood pressure and hence demonstrated some antihypertensive properties in the paediatric population tested.

It is the assessor's opinion that these results should not be totally ignored and should be reflected in section 5.1, to allow the prescriber to draw their own conclusions. This will also be in line with the SmPC Guidelines of September 2009, section 5.1 which states **"...when there are data available, but there is no authorized paediatric indication, data should be presented and a cross-reference should always be made to sections 4.2 and, as appropriate to 4.3..."**.

There are 3 proposed texts for section 5.1, one originally circulated by the Rapporteur, one by another member of state and one by the applicant, as shown below:

5.1 Pharmacodynamic properties

Text originally proposed by the assessor in the PPdAR circulated on 17 Jan 2010

In a randomised 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), a reduction in systolic blood pressure alone was noted across all treatment groups at the end of 2 weeks only. A dose response effect between groups was not seen. The reduction in diastolic pressure overall, and for each group was similar to placebo in these subjects suggesting that a dose response effect was not established. Long term effects of quinapril on growth, puberty and general development have not been studied.

Text proposed by Other member of satate

~~In a~~ **A randomised 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 DBP after 2 weeks.** ~~A sole a reduction in systolic blood pressure alone was noted across all treatment groups at the end of 2 weeks only. A dose response effect between groups was not seen. The reduction in diastolic pressure overall, and for each group was similar to placebo in these subjects suggesting that a dose response effect was not established..~~ **For systolic blood pressure (secondary criteria 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. At Weeks 2 and 8 for all patients, no significant differences in responder rates for the treatment groups were demonstrated.** Long term effects of quinapril on growth, puberty and general development have not been studied.

Text Proposed by the MAH

A randomised clinical trial using target doses of 2.5, 5, 10 and 20 mg of quinapril, in 112 children (Tanner Stage ≤ 3 , mean age 10.2 years and weight 59.5 kg) and adolescents (Tanner Stage >3 , mean age 14.3 years and weight 87.0 kg) 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 DBP after 2 weeks.

For systolic blood pressure (secondary criteria 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. At Weeks 2 and 8 for all patients, no significant differences in responder rates for the treatment groups were demonstrated.

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

Assessor's comment: taking all proposals in to consideration the assessor suggests the final text for section 5.1 below:

A randomised 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 DBP 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.

ISSUE RESOLVED.

Further Comment: It is suggested that an appropriate wording according to the Guideline on SmPC (Sept 2009) is chosen for section 4.2:

Response: The MAH agrees to add the following sentence as per the latest guideline on SmPC:

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

Assessor’s comment: MAH agrees to adapt to this suggestion on the format and appropriate wording in accordance to SmPC Guidelines of Sept 2009, for section 4.2 and their proposed wording is acceptable. **ISSUE RESOLVED.**

Conclusion

The majority of issues have been resolved.

V. OVERALL CONCLUSION AND RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy together with the assessment of the response to the list of questions raised by the Rapporteur and other MS, and taking into account the previous national assessment in the UK in Dec 2004, it is considered that the results of these studies do not support a paediatric posology. However, the incorporation of summaries of efficacy and PK findings in section 5.1, 5.2 and a cross reference in section 4.2 of the SmPC will be helpful to the prescriber.

The safety profile of quinapril generally resembles that of adults and no new adverse event (AE) or pattern of incidences in children has emerged as a result of the submitted data. No change to section 4.8 is required.

The following changes to the SmPC are recommended.

Proposed SmPC Changes

The following changes to the SmPC were proposed after assessment of the data and the MAH response (in italics and strike through):

Section 4.2:

~~Children and adolescents~~

~~There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above. (See section 5.1). There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.~~

Paediatric population

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

Section 5.1:

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), a reduction in systolic blood pressure alone was noted across all treatment groups at the end of 2 weeks only. A dose response effect between groups was not seen. The reduction in diastolic pressure overall, and for each group was similar to placebo in these subjects suggesting that a dose response effect was not established. ***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.

Section 5.2:

~~A dedicated quinapril pharmacokinetic study was conducted in paediatric patients chronically maintained on ACE inhibitors, other than quinapril, rather than healthy infants and children. Quinapril was rapidly converted to quinaprilat. Dosing on a mg/kg basis resulted in quinaprilat AUC and C_{max} values that were generally comparable across the age range of patients in this study.~~

~~The overall mean AUC_{0-∞} was 993 ng·h/mL (range: 533-1523), and mean C_{max} was 260 ng/mL (range: 70.0-445.5). Quinaprilat CL/F correlated well with body size (body surface area or weight) and creatinine clearance (mL/min). Pharmacokinetic results after a 0.2 mg/kg dose in infants and children are comparable to those observed following a 10 mg dose in adults.”~~

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 C_{max} values of quinaprilat were observed to increase linearly with increasing dose of quinapril on a mg/kg basis.”

Final outcome:

On the day 90 of the procedure, the Rapporteur's conclusions, recommendation and proposed changes to SmPC were endorsed by all concerned MSs.

The EU worksharing procedure of paediatric data for quinapril is considered finalised on the 24 March 2011. The applicant is now requested to submit:

- A type IB variation within 60 days of finalising this procedure, to update SmPC. No changes to the PIL are required.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Acequin, Recordati S.p.A, Milan; 5, 10, 20 Mg film coated tablet.

Accupro, Pfizer Limited (Brand leader); 5, 10, 20, 40 Mg film coated tablet