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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-558/S-043

Medical Review(s)



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Memorandum

DATE: 7.23.02
FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110
SUBJECT: Lisinopril Pediatric Labeling
NAME OF DRUG: Lisinopril
NDA: 19-558/S043 (Prinivil), 19-777/S044 (Zestril)

SUMMARY

This memorandum is intended to summarize the Divisional views on the lisinopril pediatric supplement, which is approvable based on the reviews summarized below. Pediatric Exclusivity for lisinopril was granted 11.19.2001. The only outstanding issues relate to agreement on the language to be included in the labeling.

DOCUMENTS USED FOR MEMO:

1. Approved labeling for Prinivil and Zestril (lisinopril).
2. Sponsor's proposed pediatric labeling for lisinopril.
3. Statistical Review of Lisinopril Pediatrics supplement by James Hung, Ph.D., dated 3.7.02.
4. Medical Review of Lisinopril Pediatrics supplement by Norman Stockbridge, M.D., Ph.D., dated 11.19.01.
5. Clinical Pharmacology and Biopharmaceutics Review of Lisinopril Pediatrics supplement by Gabriel Robbie, Ph.D., dated 6.13.02.
6. Clinical Pharmacology and Biopharmaceutics Review of Lisinopril Pediatrics supplement by Jogarao Gobburu, Ph.D., dated 6.19.02.
7. Chemistry Reviews of Lisinopril Pediatrics (2 total) supplement by Stuart Zimmerman, both dated 7.11.02.
8. Microbiology Review of Lisinopril Pediatrics supplement by Bryan S. Riley, Ph.D., dated 7.9.02.
9. Pediatric Written Request initially issued 1.21.2000.
10. Pediatric Exclusivity Determination Checklist, dated Nov. 19, 2001.

BACKGROUND

The sponsor submitted three trials in support of an indication for the use of lisinopril in children with hypertension:

- A bioequivalence study in adults, comparing the approved tablets with the extemporaneous formulation.
- A study of the pharmacokinetics of lisinopril in children aged 1 month to 16 years with GFRs >30 ml/min (Study P114).
- A controlled study measuring changes in blood pressure (BP) in children age ≥ 6 years old (Study 115). Children were randomized to receive one of three doses of lisinopril (0.625, 2.5 or 20 mg) once daily for two weeks. Following BP measurements, 50% of the children were then randomly assigned to placebo, while the remainder continued with their dose of lisinopril for an additional 2 weeks.

On the basis of these three studies the sponsor has proposed to modify the labeling for Zestril and Prinivil to:

- Reflect the pharmacokinetic and clinical results.
- Describe the extemporaneous formulation.

LISINOPRIL PEDIATRIC TRIAL REVIEWS

Details of the review of these trial are to be found in the review by Drs. Stockbridge, Hung, Robbie and Gobburu. The sections will highlight relevant findings from these reviews.

ANTI-HYPERTENSIVE EFFICACY

I won't summarize the findings from the clinical and statistical reviewers in detail. The following can be drawn from their reviews

- 1) In study 115, BP was reduced in all dose groups, but in the absence of a placebo group no absolute effect on BP could be determined. There was, importantly, a highly significant relationship between increasing dose of lisinopril and increased antihypertensive efficacy (see Dr. Stockbridge's review, page 11 and Dr. Hung's review page 7).
- 2) During the withdrawal phase of study 115, children randomized to placebo had a significantly greater increase in BP than children randomized to continued therapy, again supporting an antihypertensive effect of the 2.5 and 20 mg doses (see Dr. Stockbridge's review, page 11).
- 3) While the demographic subgroups were small, limiting power to detect differences, there were no apparent striking interactions of race, gender or Tanner stage with antihypertensive effect of lisinopril. Dr. Hung, like the Biopharmaceutics reviewers, concluded that there was an interaction between the child's weight and antihypertensive efficacy. In general, the heavier children had a flatter dose-response curve and a smaller maximal antihypertensive effect (see Dr. Hung's review page 8).
- 4) The Biopharmaceutics reviewers (Dr. Robbie and Gobburu) were able to derive a PK/PD relationship between dose of lisinopril and the mean change in BP, based on the data from study 115, further supporting the efficacy of lisinopril in this population. Their comments on the interaction between weight and antihypertensive efficacy can be found beginning on page 32) of their review.

SAFETY

The medical reviewer, Dr. Stockbridge, concluded that no new safety concerns were identified in the pediatric population relative to the adult population where amlodipine has been used extensively. This conclusion was based on the data from the clinical trials submitted in the supplement (section 2.3.4.3 of his review) as well as a review of the papers cited by the sponsor and on data submitted from a Belgian nephrology clinic in which 123 patients received lisinopril over a 9-year period.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The Biopharmaceutics reviews by Drs. Robbie and Gobburu are to be referred to for details. Relevant aspects of the pharmacokinetics and the PK/PD modeling performed by Dr. Gobburu is included in the Efficacy section above. The reviewers concluded that there was a demonstrated dose-response relationship for reduction in seated systolic blood pressure (BP) for children aged >6 years old. In the absence of a placebo group, the absolute effects of the various doses on BP cannot be determined. The magnitude of the antihypertensive effect varied with subject weight (see page 2 of his review for a summary and page 41 for details), but in all weight groups there was a significant relationship between increasing dose and decreasing BP. The relationship between dose and change in BP is best described using a linear fit, an observation that is at odds with the standard modeling for BP (which would predict an Emax model), but is not relevant to the approval decision.

With regard to the pharmacokinetics of lisinopril in children <6 years of age, the sponsor performed two important tasks that materially strengthen the case for description of the information in label. First, they developed and characterized an extemporaneous formulation. Production of this formulation is described in Dr. Robbie's review on page 3, and includes the dissolution of lisinopril tablets in water followed by the addition of Bicitra and Ora-Sweet, followed by storage at or below 25 degrees Centigrade for up to 4 weeks. This formulation was demonstrated to be bioequivalent to the lisinopril tablets (see Biopharmaceutics review page 21) and found to be stable (see Chemist's review above). The second important task performed by the sponsor was to conduct a robust examination of the pharmacokinetics of the solution in children ranging from 6 months to 6 years, with 6 children <2 years of age being studied. The only limitation to these data was the absence of children with significant renal disease, but this degree of rigor with regard to the pharmacokinetics of lisinopril in the very young is materially useful. The results of this testing (see table on page 26 of Dr. Robbie's review) is that the clearance of lisinopril is similar across the age groups studied when corrected for body surface area. The kinetics of lisinopril also appeared to be similar to historical adult kinetic data (see page 27).

CHEMISTRY, PHARMACOLOGY/TOXICOLOGY

The sponsor submitted chemistry information regarding the extemporaneous formulation preparation of lisinopril. This suspension, per the chemist, could be reproducibly made using the instructions developed by the sponsor from individual lisinopril tablets. The drug then remains dissolved in the suspension matrix over the recommended use time of 4 weeks, and demonstrates adequate stability when stored at room temperature. Antimicrobial testing indicates that the suspension meets the requirements for the use of extemporaneous formulation. The Chemist recommended the inclusion of the suspension in approved labeling.

No Pharmacology/Toxicology review was required for this submission.

CONCLUSIONS

The antihypertensive efficacy of lisinopril in the pediatric population >6 years of age is adequately demonstrated by the trials submitted by the sponsor (study 115). The available data are sufficient for inclusion in label in the Clinical Trials section. The pharmacokinetics of lisinopril in children between 1 month and 16 years of age has also been studied, including 6 children <2 years of age (study 114). Overall, the clearance of lisinopril was similar across all of the age groups when adjusted for body surface area. These data are robust and relevant to the use of the extemporaneous formulation, supporting their inclusion in the label. There only remaining issues revolve around the appropriate labeling of lisinopril for pediatrics.

Proposed pediatric indication for lisinopril

The antihypertensive effect of lisinopril should be described in the Clinical Trials section. The efficacy as an antihypertensive in the pediatric population is not a novel indication.

Inclusion of PK language for children < 6 years of age

In the absence of any clinical data demonstrating the antihypertensive efficacy of lisinopril in children <6 years old, I believe the decision to include this information should be based on two principles: a consideration that no data exists from the trials or other sources that indicate the drug is ineffective in children <6, and the conclusion that the pharmacokinetics of the drug have been adequately characterized in the children <6. The latter piece is of particular importance if the drug is excreted by the kidneys, as children <1 year of age have significantly different renal function than older children and adults due to incomplete renal maturation. If either piece is missing, the labeling should be silent about the observed pharmacokinetic data.

For lisinopril, the sponsor has conducted a significant exploration of the pharmacokinetics of lisinopril in this age group, including the development of an extemporaneous formulation to assist the potential use of lisinopril in children too small to swallow tablets. The Biopharmaceutics reviewers are in agreement as to the robust nature of these data, and in the appropriateness of their inclusion into the label. Significant limitations exist that need to be included: the absence of antihypertensive efficacy data in children <6 years old, and the absence of data in children with renal impairment. The latter is relevant given that lisinopril is renally excreted.

Description of the antihypertensive effect of lisinopril

Dr. Stockbridge has proposed language describing the antihypertensive effects of lisinopril that accurately describes the antihypertensive effects of lisinopril in this population. This is a robust investigation; this should be adequately reflected in the labeling.

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/s/

Doug Throckmorton
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MEDICAL OFFICER

2 Labeling

The sponsors propose inclusion of a description of the study results in the labels for lisinopril.

Under CLINICAL PHARMACOLOGY, there is a new section, as follows:

Pediatric Patients

[

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The first two paragraphs should be rewritten as follows:

Pediatric Patients: A study of 52 hypertensive patients age 6 months to 16 years, with no more than moderate renal impairment, demonstrated a similar pharmacokinetic profile to that reported for normal adults. After doses of 0.1 to 0.2 mg/kg, about one-fourth of the administered dose was recovered from urine.

Clinical Study: In a clinical study involving 115 hypertensive pediatric patients five to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of lisinopril daily. Lisinopril doses >0.625 mg administered once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive effect of lisinopril was consistent across all subgroups (age, Tanner stage, gender, race). In this study, lisinopril was generally well tolerated.

The sponsors propose the following in the section on PRECAUTIONS:

Pediatric Use

This section should be rewritten as follows:

Pediatric Use

Antihypertensive effects of {TRADENAME} have been established in hypertensive pediatric patients aged 6 to 16 years. There are no data on the use of {TRADENAME} in neonates or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m² as no data are available.

The sponsors propose a new paragraph under ADVERSE REACTIONS:

Pediatric Patients: The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

This is adequate.

Under DOSAGE AND ADMINISTRATION, the sponsors propose the following:

There are no data relating to effectiveness in pediatric patients less than 6 years old.

The sponsor proposes a new section of DOSAGE AND ADMINISTRATION:

Pediatric Hypertensive Patients

The usual recommended starting dose is 0.07 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY, Pediatric Patients.

{TRADENAME} is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m² as no data are available.

Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)

*Add 10 mL of Purified Water USP to a polyethylene terephthalate (PET) bottle containing ten 20-mg tablets of {TRADENAME} and shake for at least one minute. Add 30 mL of Bicitra[®] ** diluent and 160 mL of Ora-Sweet SF[™] *** to the concentrate in the PET bottle and gently shake for several seconds to disperse the ingredients.*

The suspension should be stored at or below 25°C (77°F) and can be stored for up to four weeks. Shake the suspension before each use.

This is adequate.

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3 Clinical studies

3.1 Protocol P114: An open-label study to investigate the pharmacokinetics of lisinopril in hypertensive children and infants.

3.1.1 Study dates

March 2000 to February 2001

3.1.2 Source materials reviewed

Final study report

Fully amended protocol and amendments

3.1.3 Protocol

This was an open-label study of PK in children 1 month to 16 years, with history of hypertension and GFR >30 mL/min/m². Subjects were dosed at 0.15 mg/kg/day for 7 days with PK sampling performed on day 7 at times 2, 4, 6, 8, 10, 12, 16, and 24 hours after the last dose (fewer samples in children <4 years old). Conventional safety monitoring was employed.

Study drug was lisinopril 20-mg tablets suspended in sterile water, citrate buffer, and syrup base.

3.1.4 Results

3.1.4.1 Conduct

The study was conducted at sites in the US (5), Chile (1), and Peru (1). Sites enrolled 2 to 16 subjects.

Eleven to 17 subjects per age cohort were enrolled; PK data were obtained for 8 to 17 per cohort.

One subject discontinued for other than an adverse event.

3.1.4.2 Pharmacokinetics

The sponsor's analyses of PK data are shown in Table 2.

Table 2. Pharmacokinetic results (P114)

	< 2 years	2-6 years	6-12 years	12-16 years
Mean dose (mg/kg)	0.15	0.15	0.15	0.15
AUC ₀₋₂₄ ng.h/mL/m ²	101	84	129	117
C _{max} ng/mL/m ²	7.2	6.1	10.1	9.3
Median T _{max}	5	5	5	6

3.1.4.3 Safety

There were no deaths and no withdrawals for adverse events.

Twenty-two subjects reported adverse events, two of which (a sickle cell crisis and a urinary tract infection) were considered serious. Four subjects had minor lab abnormalities. None of the reported adverse events bore any likely relationship to study participation.

3.1.5 Summary

After correction for body surface area, dosing at 0.15 mg/kg resulted in similar gross pharmacokinetic parameters (AUC, C_{max}, T_{max}) in cohorts <2 years old, 2-6 years old, 6-12 years old, and 12-16 years old, all with normal or near normal renal function. This study raises no safety issues regarding use in these age groups.

3.2 Protocol P037: An open, two-period crossover study to determine the relative bioavailability of lisinopril suspension 20 mg and marketed PRINIVIL™ 20-mg tablets

3.2.1 Study dates

October - December 1999

3.2.2 Source materials reviewed

Final study report

Fully amended protocol and amendments

3.2.3 Protocol

This was an open-label, single center study in 25 normal adult male and female subjects, age 18-45, and within 20% of ideal body weight. On two study days separated by at least 21 days, subjects received, in random order, a single dose of lisinopril 20 mg as a tablet of the commercial formulation or a suspension of the tablet in citrate buffer plus syrup. Blood and urine samples were collected over 96 hours after dosing. Conventional safety monitoring was employed.

3.2.4 Results

3.2.4.1 Conduct

The 25 subjects, 14 males and 11 females, were enrolled at a single center. The age range was 20 to 45. Twenty-two subjects were Hispanic.

Twenty-four subjects completed both treatment phases. One subject withdrew for a reason other than adverse events.

3.2.4.2 Pharmacokinetics and pharmacodynamics

Plasma levels of lisinopril for the two treatment phases are shown in Figure 1.

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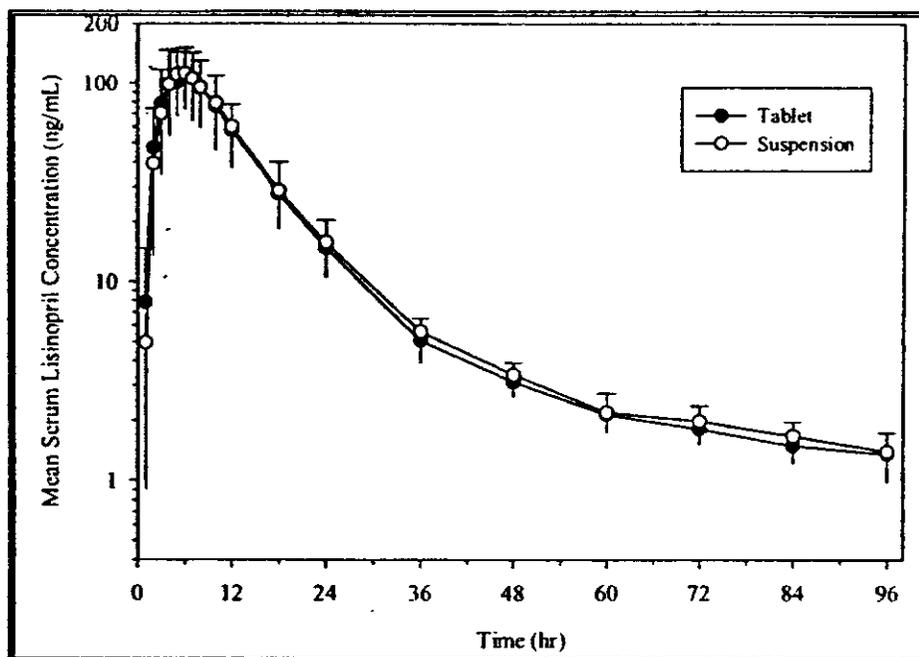


Figure 1. Plasma levels of lisinopril (P037)

Plasma levels of lisinopril were very similar following administration of tablet and suspension. Confidence limits around the pharmacokinetic parameters (AUC, C_{max}, T_{max}) excluded that these parameters were as much as 20% different.

3.2.4.3 Safety

There were no deaths.

Six subjects reported adverse events, generally headache and dizziness. One subject had reported coronary insufficiency, probably an unsuspected pre-existing condition. No other serious adverse events were reported.

3.3 Protocol P115: A double-blind, randomized, dose-response study of lisinopril in children with hypertension.

3.3.1 Study dates

February 2000 - March 2001

3.3.2 Source materials reviewed

Final study report

Fully amended protocol and amendments

3.3.3 Protocol

This was a double-blind, multi-center study in which children 6 to 16 years old, with hypertension (>95% for age and sex) were randomized to lisinopril 0.625, 2.5, or 20 mg¹ once daily for two weeks after which subjects were randomized to continue the same dose or to placebo for another 2 weeks. Subjects in the high-dose group received one-half that dose on the first 2 days. The primary end point was the change in seated diastolic pressure at the end of the first 2-week treatment period. The change in diastolic blood pressure during the placebo withdrawal period was a secondary end point. Conventional safety monitoring was employed.

¹ Subjects >50 kg received double the nominal dose.

3.3.4 Results

3.3.4.1 Conduct

One hundred fifteen subjects were enrolled at 13 sites in the US, 2 in Mexico, and one each in Belgium, Canada, Argentina, Brazil, Chile, Columbia, and Venezuela. Sites enrolled 1 to 15 subjects.

One hundred four subjects completed the first phase and entered the placebo-withdrawal phase. Seven of the 12 withdrawals were for lack of effectiveness; two were for adverse events.

Demographic and baseline characteristics are shown in Table 3.

Table 3. Demographics and baseline characteristics (P115)

	Lisinopril dose		
	Low N=33	Med N=24	High N=58
Male (%)	64	63	67
Caucasian (%)	46	46	43
Hispanic	42	42	47
Other	12	13	10
Age <6 (%)	3	0	2
6 to 13	49	46	43
13 to 16	49	54	55
Mean BP (mmHg)	126/88	124/91	129/90

Subjects in the various treatment arms were fairly well matched at baseline.

Subjects had a rich variety of secondary diagnoses, particularly renal disease; these were reasonably well matched in the various groups. Most subjects had received prior treatment for hypertension; the most common prior therapies were ACE inhibitors and calcium channel blockers.

There were a small number of protocol violations.

3.3.4.2 Results

Changes in seated diastolic pressure by dose and weight strata are shown in Figure 2. For the intent-to-treat population, the mean change in each dose group was statistically significantly different from placebo, the responses increased monotonically with dose, and the slope of the dose-response curve was statistically significantly different from zero.

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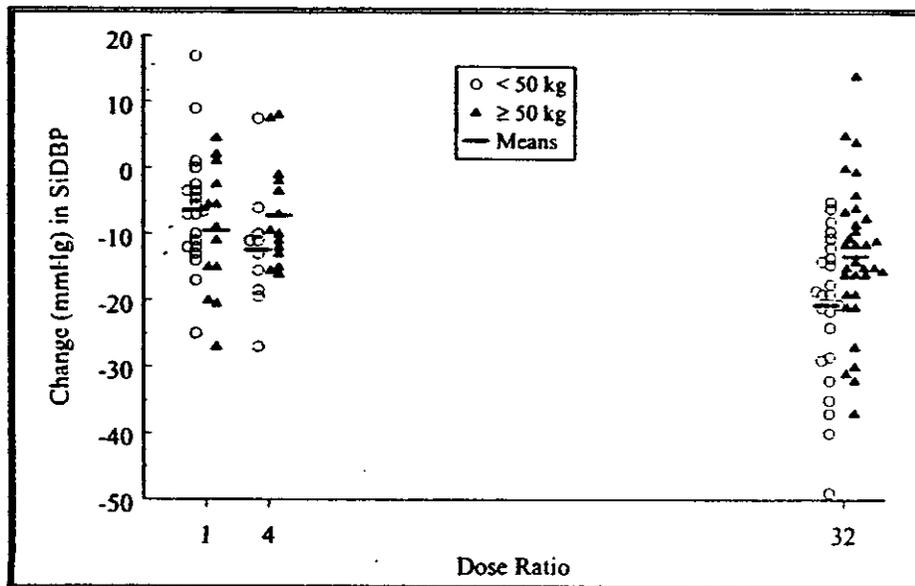


Figure 2. Changes in seated diastolic pressure during phase I (P115)

Subgroup analyses by age, Tanner stage, sex, and nationality revealed no striking dissimilarities, but some of these comparisons had little discriminatory power. The response was somewhat less in Blacks than in Caucasians or others; similar to the situation in adults. The slope was somewhat less for children >50 kg compared with children <50 kg.

The change in diastolic pressure from the end of phase I to the end of the placebo-withdrawal period is shown in Figure 3.

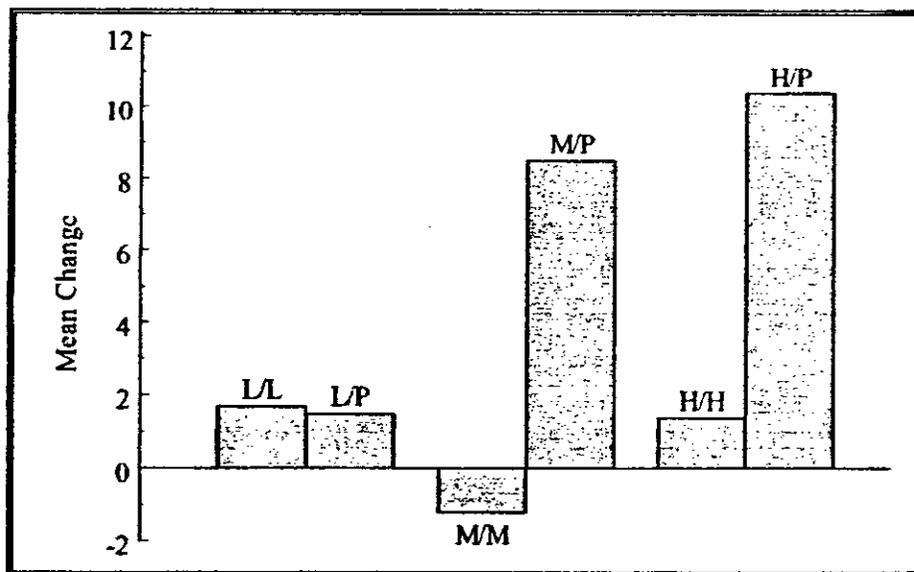


Figure 3. Changes in seated diastolic pressure during phase II (P115)

For the middle and high doses, the increases in seated diastolic pressure were large, consistent with the non-placebo-controlled results in the first phase.

During phase I, the change in seated systolic pressure also decreased monotonically with dose, from -5 mmHg on the low dose to -15 mmHg on the high dose.

3.3.4.3 Safety

There were no deaths.

There was one non-serious adverse event leading to withdrawal (paresthesia and pharyngeal hyperemia) and two subjects had serious adverse events (pneumonia and gastroenteritis) that did not lead to withdrawal. Adverse events were reported for 45 to 63% of subjects per group, with no apparent relationship to dose.

Another 5 serious adverse events have been reported during open-label follow-on experience (exposure unclear from study report). These events were pneumonia, seizure disorder (pre-existing), bronchospasm (pre-existing), intentional overdose, and nephrotic syndrome (pre-existing).

The most common adverse event was headache (about 5% overall, with no apparent relationship to dose).

Five to 24% of subjects per arm had laboratory abnormalities reported; one of which (creatinine rise from 1.7 to 2.2 mg/dL) led to discontinuation. No single laboratory abnormality was reported by as many as 3 subjects.

3.3.5 Summary

Lisinopril doses between 0.625 and 20 mg per day were clearly antihypertensive in children age 6 to 16. The treatment effect increased monotonically with dose. There were no novel problems with tolerance or safety.

3.4 Other published data

The sponsors have reviewed the literature for the use of lisinopril in children. The reports are not summarized in this review as they are anecdotal in nature and non-contributory to the safety and effectiveness in children with hypertension.

The sponsors also report upon the use of lisinopril in Belgian pediatric nephrology clinic. One hundred twenty-three of these patients received lisinopril over a 9-year period. The doses were in the range of the middle to high doses of the sponsors' controlled study. There were 5 deaths, described only as not related to lisinopril, and fifteen uncharacterized serious adverse events, only one of which (tachycardia) was considered possibly treatment-related. Five patients discontinued for unspecified adverse events. The most common "adverse event" was hypotension. There were no reported cases of angioedema.

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4 Summary and recommendations

The studies clearly satisfy the terms of the Written Request. Thus, a decision to grant exclusivity is appropriate.

Moreover, lisinopril is clearly effective in reducing blood pressure in children with hypertension, and a description of these findings in labeling is appropriate.

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Norman Stockbridge
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