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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-998/S-059

Pediatric Data Review

U.S. PUBLIC HEALTH SERVICE

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Pediatric data Review

JUN 2 6 2000

NDA: 18-998
Drug: enalapril maleate
submission: 1/14/00

review last revised: 6/26/00

1. Background

The data derive from a research program elicited by a Written Request which sought guidance for the use of enalapril to reduce blood pressure (BP) in hypertensive pediatric patients. Neonates were not evaluated, with the sponsor's expressed rationale being that the antihypertensive therapeutic needs of this age group are typically for short-acting intervention rather than for an oral preparation such as the one under consideration here.

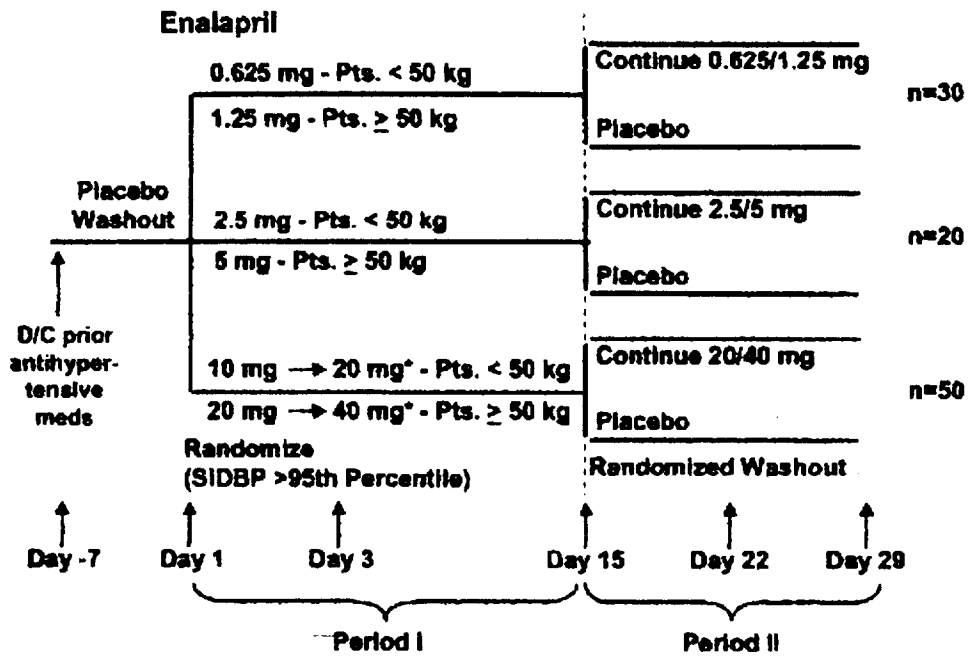
2. Study P167C

2.1 Design

This was a double-blind, randomized dose-response study of enalapril in 110 hypertensive children aged 6-16 years. Any prior antihypertensive therapy was discontinued and the patient was entered into the double-blind when his or her sitting diastolic BP (SiDBP) was higher than the 95th percentile level for the patient's age, gender, and height. As shown in the figure below, patients were stratified by weight (<50 vs ≥50 kg) and randomly allocated to 1 of 3 titrated once-daily treatment groups for 14 days (Period I). Patients who weighed <50 kg received enalapril 0.625 mg/d (low dose), 2.5 mg/d (middle dose), or 20 mg/d (high dose). Patients who weighed ≥ 50 kg received enalapril 1.25 mg/d (low dose), 5 mg/d (middle dose), or 40 mg/d (high dose). The allocation ratio was 1: 4: 32 for the low : middle :high groups, respectively.

Figure: 1

Design of treatment arms in study P167C



source: scan of figure 1

Patients were titrated at day 3 unless limited by an adverse experience or excessive hypotension. Those in the high-dose groups had dose doublings on day 3, while those in the other dosage groups had blinded mock dose titrations. The lowest dosage, or placebo for same, was administered as an enalapril suspension prepared in a double-blind manner at the study site.

After 14 days of treatment, patients were randomly allocated (by pre-randomization[1] rather than re-randomization) to either continue their dose for another 14 days, or to switch to placebo. This blinded withdrawal period (Period II) lasted for 14 days or to the time point at which the patient's trough SiDBP returned to the pre-treatment level, whichever occurred first. At the completion of the double-blind study, patients could continue in an optional, open-label, 6-month extension.

The primary objective was to determine the change from pre-treatment SiDBP at trough after 2 weeks.

2.2 Efficacy Results

A total of 110 hypertensive pediatric patients were studied. The maximum enalapril dose of 20-40 mg amounted to an average of 0.58 mg/kg on a per weight basis. The following was the distribution of pre-treatment covariates:

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[1] i.e. randomized according to the original allocation number assigned on day 1.

Table: 1

Enalapril Pediatric Dose Response Study—Patient Characteristics

	Low Dose 0.625/1.25 mg (N=30) n (%)	Middle Dose 2.5/5 mg (N=30) n (%)	High Dose 20/40 mg (N=50) n (%)	Total (N=110) N (%)
Age (Years)				
6 to 12	16 (53.3)	17 (56.7)	23 (46.0)	56 (50.9)
13 to 16	14 (46.7)	13 (43.3)	27 (54.0)	54 (49.1)
Mean	11.4	11.5	11.8	11.6
SD	2.7	3.1	3.3	3.1
Median	12.0	12.0	13.0	12.0
Range (male)	6 to 16	6 to 16	7 to 16	6 to 16
Range (female)	6 to 14	6 to 16	6 to 16	6 to 16
Tanner Stage				
≤3	20 (69.0)	21 (70.0)	29 (58.0)	70 (64.2)
>3	9 (31.0)	9 (30.0)	21 (42.0)	39 (35.8)
Gender				
Male	20 (66.7)	22 (73.3)	22 (44.0)	64 (58.2)
Female	10 (33.3)	8 (26.7)	28 (56.0)	46 (41.8)
Race				
White	10 (33.3)	14 (46.7)	19 (38.0)	43 (39.1)
Black	6 (20.0)	9 (30.0)	8 (16.0)	23 (20.9)
Hispanic	14 (46.7)	7 (23.3)	23 (46.0)	44 (40.0)
Country				
U.S.	14 (12.7)	19 (17.3)	21 (19.1)	54 (49.1)
Non-U.S.	16 (14.5)	11 (10.0)	29 (26.4)	56 (50.9)
Note: Tanner stage was not recorded in 1 patient assigned to the low-dose group.				

[P167C]

source: scan of table 3

With respect to change from pre-treatment SiDBP after 2 weeks at trough (24 hours postdose), there was reported a statistically distinguishable dose-response relationship between the lowest dose of 0.625 mg/ 1.25 mg and each of the higher doses (2.5 mg/ 5 mg and 20 mg/ 40 mg), resulting in a slope of -0.3 mm Hg per unit increase in dose ratio (1: 4: 32 in the low-: middle-: high- dose groups, respectively), and a p value < 0.001. Mean BP reductions at trough after 2 weeks were 6.3, 8.9, and 14.9 mmg Hg respectively. Shown below are these results.

Table: 2

Mean trough levels and changes from pre-treatment SiDBP after 2 weeks, at trough (intention-to-treat)

	Low Dose (0.625/1.25 mg)	Middle Dose (2.5/5 mg)	High Dose (20/40 mg)
N	30	29	50
Mean (SD) baseline sitting blood pressure	88.1 (8.4)	88.9 (8.0)	90.9 (9.5)
Mean Change (SD)	-6.3 (7.8)	-8.9 (8.7)	-14.9 (8.7)

N = Patients with both baseline (on Day 1) and postdose measurements.
Mean Change = Measurement on Day 15 - Measurement on Day 1.
[P167C]

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This negative slope for dose-response was consistently observed across subgroups of age, Tanner Stage, gender, race, and country.

In Period II approximately half of the patients continued enalapril treatment while the rest were switched to placebo. As shown in the table below, BP in the placebo group increased after discontinuation of therapy. The overall mean difference between the placebo group and the pooled enalapril group was 6.1 mm Hg ($p < 0.003$), however the low dose did not evidence an appreciable increase in BP post-withdrawal.

Table: 3

Mean changes from day 15 trough SiDBP at end of withdrawal (intention-to-treat)

Treatment Group (Period I/Period II)	N	Mean Change (SD)	Group Difference
Low dose/Low dose	12	1.3 (8.9)	
Low dose/Placebo	15	1.7 (7.9)	0.5
Middle dose/Middle dose	14	3.8 (7.1)	
Middle dose/Placebo	11	10.5 (10.1)	6.8
High dose/High dose	25	-2.3 (10.2)	
High dose/Placebo	24	8.8 (10.6)	11.0

N = Patients with both baseline (on Day 15) and postdose measurements.
Mean Change = Last Measurement of Period II - Measurement on Day 15 of Period I.
Group Difference = Placebo - Enalapril.
[P167C]

source: scan of table 5

The post-withdrawal increase BP occurred in all subgroups (age, Tanner Stage, gender, race, and country). There was a trend towards younger children and those with Tanner stage ≤3 rebounding faster than older children.

Qualitatively similar findings were reported with respect to systolic BP. Enalapril produced a statistically distinguishable dose-dependent reduction in trough sitting systolic BP (with mean changes being -7.1, -6.6, and -12.5 mm Hg in the low-, middle-, and high- dose groups, respectively). There was an increase in trough sitting systolic BP when patients were placebo withdrawn, especially in the middle- and high- dose groups, in which differences in mean changes were 9.9 and 11.2 mm Hg, respectively.

3. Safety at large

The sponsor report on safety data obtained from the above dose-response study, a pediatric PK Study,[2] the sponsor's adverse event (AE) database, a literature review, and a clinical chart review study.

3.1. from Study P167C

No patients died during this study. Two enalapril-exposed subjects discontinued as a result of a clinical AE. One (AN 6041, male, 15 years) experienced hypotension on the 7th day of treatment with enalapril 40 mg. The other patient (AN 5114, male, 7 years) experienced a relapse of nephrotic syndrome. The most common laboratory change was an increase in serum potassium.

3.2 from pediatric PK study

Five of 40 patients reported clinical AE and 2 had laboratory AE during or following enalapril therapy. None were investigator-attributed as drug related, and none caused discontinuation. One 3 year old patient (with history of ischemic encephalopathy and febrile seizure) had a febrile seizure 2 days after completion of the study. Another (a 24 month old with history of pre-treatment bronchitis) was hospitalization with bronchopneumonia on day 7. The overall reported AE were headache, parotitis, asthma exacerbation, herpes simplex, febrile convulsion, bronchitis, bronchopneumonia, decreased hemoglobin, increased eosinophils.

3.3 from worldwide AE database

The sponsor examined their worldwide database for reports[3] in children up to 16 years. These findings suggest that the AE profile in children is not different from that seen in adults. There were 9 reports of deaths, primarily in very young children (4-56 days) with significant underlying cardiac disease.

3.4 from Literature review

A clinical literature review was conducted by Drs. Ingelfinger and Wells. These findings suggested that the AE profile in children was not different from that seen in adults. They found 69 literature citations of the use of enalapril in children in studies involving more than 600 children, including those with renal or renovascular disease. A formal meta-analysis was not undertaken, because of the heterogeneity of study designs. In children older than neonates, the usual initial therapy was 0.05 to 0.10 mg/kg once or twice daily. Maximum single doses of approximately 0.5 mg/kg were used, but dosages over 0.8 mg/ kg/d were rarely used.

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[2] study P168C.

[3] i.e. those reports received on or before 9/30/99.

3.5 from Chart Review Study

A clinical chart review of long-term safety was performed on medical records from a pediatric nephrology referral practice. These findings suggested that the AE profile in children was not different from that seen in adults. A total of 184 children (105 male, 79 female) were identified in this practice. Enalapril (or enalaprilat) was being used to treat hypertension in about 81% of the children, while in the remaining 19%, treatment was proteinuria with or without hypertension. Most of the children (82.6%) had renal disease. The median duration of treatment was 401 days. The median daily starting dose of enalapril was 0.17 mg/kg/d (range 0.08 to 0.29 mg/kg/d) for the 134 patients for whom such data were available. Drug-related AE numbered 22, of which 1 was deemed serious (a case of worsening of renal impairment that required hospitalization). There were 73 reports of cough, and no reports of angioneurotic edema. Growth as measured by percentile of weight and height for age was not adversely affected by enalapril.

4. Comments

The findings obtained in response to the Written Request suggest that the AE profile in children was not different from that seen in adults, and these findings are adequately described in the proposed labelling.

/S/

Steven Mark Rodin, M.D. Date
Medical Officer

attachment: proposed labelling

cc: HFD-110/ division file, CSO, A.Karkowsky, **no copy to Rodin**

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1 pages redacted from this section of the approval package consisted of draft labeling