CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-998/S-059

Medical Review

U.S. PUBLIC HEALTH SERVICE

Steven Mark Rodin, M.D.
Medical Officer

Food Drug Administration
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products

Addendum to review of Pediatric Exclusivity request

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

review last revised: 4/28/00

This is a clarification of my original review. In the Written Request dated 9/8/99[1] guidance was sought for the use of enalapril maleate to reduce blood pressure (BP) in hypertensive pediatric patients. Based on the requested data, the sponsor was to propose labeling changes that they consider to be warranted. No new indication was to be recognized in the studied population of pediatric patients with essential hypertension.

The proposed label, on its face, is responsive to the Written Request. No new indication is sought.

/S/

Steven Mark Rodin, M.D.
Medical Officer

4/28/00
Date

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

[1] this superceded the Written Request of 12/23/98.

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U.S. PUBLIC HEALTH SERVICE

APR 1 3 2000

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Food Drug Administration
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products

Medical Evaluation of Pediatric Exclusivity request

NDA: 18-998
Drug: enalapril maleate
review last revised: 1/31/00

1. ~**Summary of Written Request dated 9/8/99**[1]:

In the Written Request guidance was sought for the use of enalapril maleate to reduce blood pressure (BP) in hypertensive pediatric patients. A program considered responsive to the request was to have the following features:

1.1 `**general aspects of design and results**:

- a dose-ranging efficacy data from a randomized, double-blind, parallel group study employing weekly followup during two weeks of treatment. No placebo or placebo withdrawal was required[2].

- safety data from the dose-ranging trial, and either an open-label extension of the dose-ranging trial or from another comparable database, and safety data summarization of all available information in pediatric patients.

- efficacy results must be interpretable (although no demonstration of efficacy was required). Nonplacebo trials would prove uninterpretable (and thus be considered *not* responsive to the request) if certain outcomes arise. Specifically, if in a nonplacebo trial the observed dose-response was found to be horizontal one could not distinguish between doses that all lay at the flat *upper* part of the dose-response curve (and are thus equally effective) vs doses that all lay at the flat *lower* part of the dose-response curve (and are thus ineffective).

1.2 `**population characteristics**:

- effectiveness studies should include a reasonable proportion (not defined) of pre-pubertal children.
- a mixture of (not defined) of black and non-black patients.
- patients of both sexes in one or more of the pediatric age groups defined above
- at least 50% of the patients in the trial should be 6 – 12 years old or ≤ Tanner Stage 3 or younger.

1.3 `**statistical considerations**:

[1] this superceded the Written Request of 12/23/98.

[2] if a randomized placebo withdrawal design were pursued, patients would need be force-titrated to maximal tolerated doses of enalapril and then withdrawn to lower doses (including placebo).

- adequate sample size[3] basis on a power calculation which employs a realistic estimate of effect size, ≥80% power, and alpha level of 0.05.

1.4 **pharmacokinetic (PK) data**:

- PK data (from the dose-response trial, stand-alone PK studies or from safety studies) is to be obtained in subjects with grossly normal metabolic function whose ages fall into the following groups[4]: infants and toddlers (age 1 to 24 months), pre-school children (age 2 to 6 years), school-age children (age 6 to 12 years or ≤ Tanner Stage 3), and adolescents (> 12 years or > Tanner Stage 3 to 16 years).
- use of age-appropriate formulations; characterize bioavailablility relative to the marketed product.
- For the parent drug, and each metabolite that makes a substantial contribution to efficacy and/or toxicity, estimates of AUC, half-life, C_{max}, and t_{max} should be obtained.
- PK evidence that the doses studied place patients in the range of blood levels attained in adults. [they report that in the pediatric group at steady state the mean enalaprilat $AUC_{0\text{-}24\ hr}$ ranged from 204-305 ng-hr/mL, and mean enalaprilat C_{max} ranged from 21-28 ng/mL. In 12 adult volunteers the mean steady state enalaprilat $AUC_{0\text{-}24\ hr}$ and C_{max} was 316 ng-hr/mL and 39 ng/mL, respectively].

1.5 **Labelling changes**:

- based on the requested data, the sponsor should propose labeling changes that they consider to be warranted.

- no new indication would be recognized unless safety and efficacy is demonstrated in a population that (apart from age) is distinct on some etiologic or diagnostic basis, relative to the approved adult population[5].

2. **Conclusion:**

The data, on their face, are responsive to the Written Request.

The doses studied place patients approximately in the range of blood levels attained in an historical adult control: in the pediatric group at steady state the mean enalaprilat $AUC_{0\text{-}24\ hr}$ ranged from 204-305 ng-hr/mL, and mean enalaprilat C_{max} ranged from 21-28 ng/mL. In 12 adult volunteers the mean steady state enalaprilat $AUC_{0\text{-}24\ hr}$ and C_{max} was 316 ng-hr/mL and 39 ng/mL, respectively.

/S/

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Medical Officer

1/31/00
Date

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[3] for randomized placebo-controlled withdrawal designs this refers to the sample size during the withdrawal phase.

[4] neonates (age less than one month) were not requested to be part of kinetic studies.

[5] Pediatric hypertension secondary to advanced renal disease would be one such distinct population.

BONGIOVANNI,

MAR 16 1999

Medical Review

IND # [redacted]	IND Volume: 134.1	Drug Name: enalapril
Sponsor: Merck	Type of Document: statistical analysis plan for pediatric study	Reviewer: Ganley
Correspondence Date: 2/16/99	Date Received: 2/17/99	Date Completed: 3/16/99

The submission includes an updated statistical analysis plan for study 167. Study 167 is a randomized, double-blind, parallel dose trial in pediatric hypertensive patients. The trial consist of a 2 – 7 day washout period, a 2 week double blind treatment period, a 2 week placebo withdrawal phase and an optional open label 6 month treatment phase. The study will randomize 100 patietns to enalapril 0.625/1.25 mg (N = 30), 2.5/5.0 mg (N = 20) or 20 /40 mg (N = 50). The dose received by patients is dependent on the weight of the patients. Patients < 50 kg will receive the lower dose of a dose group while patients ≥ 50 kg will receive the higher dose of a dose group. Table lists the analysis plan for the endpoints.

Table 1. Analysis Plan

Endpoint	Analysis
Slope of the siDBP vs. dose.	• Simple regression with dose index as a continuous variable
Mean change in siDBP between each active treatment arm and the corresponding placebo arms	• One way ANOVA with a factor of 6 treatment arms • t-test

The sample size is based on an $\alpha = .05$, power = .85 to detect a 5 mm Hg difference (s.d. = 8 mm) between extreme doses. The power of the randomized washout period is .87 ($\alpha = .05$, 5 mm Hg difference). The power of the washout period is based on all randomized patients entering the washout period.

Impression

The Written Request for pediatric studies in hypertension requires that the sample size for the withdrawal phase be adequate. For this study, the power calculation for the withdrawal phase assumes that there will be no dropouts in the double-blind, parallel dose treatment phase. This is unrealistic.

The withdrawal phase data becomes relevant from a regulatory viewpoint only if a zero slope is obtained in the first treatment phase. In the event of a zero slope, the number of patients who enter the withdrawal phase should provide sufficient power (0.80) to interpret the study. If there are a significant number of dropouts, then this study may be deemed not interpretable because of insufficient power.

Regulatory Action

The protocol should be designed to insure that power is maintained in the withdrawal phase in the event there are a significant number of withdrawals during the first treatment phase.

Charles J. Ganley, M.D.

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HFD-710/hung

K Hong Graham

MAR 12 1999

Medical Review

IND # [redacted]	Sponsor: Merck	IND Volume: 134.1
Drug Name: enalapril	Type of Document: protocol	Medical Reviewer: Ganley
Correspondence Date: 12/28/98	Date Received: 1/5/99	Date Completed: 3/8/99

The sponsor submits a protocol to study enalapril in pediatric patients. This is the primary study to support the 6 month exclusivity extension for enalapril.

Protocol 167

This is a randomized, double-blind, parallel dose study in pediatric hypertensive patients. The primary objective is to explore the dose response relationship of enalapril in children. The study will include patients > 20 kg, age 6 – 16, males and females with a mean siDBP > 95th % based on gender, age and height. GFR should be > 30 ml/min/1.73 m^2 (by the Schwartz formula[1]). The study hopes to enroll 10% - 30% African American, 25% - 50% female and 50% in the 6 – 12 (or Tanner stage 3). Patients are excluded if they have severe or symptomatic hypertension, heart failure, organ transplantation, significant diseases involving other organ systems, clinically significant lab abnormalities, heart block, atrial fibrillation, atrial flutter, significant bradycardia or sick sinus syndrome.

The trial consists of a 3 to 7 day washout period, a 14 day double blind treatment period, a 14 day placebo controlled withdrawal period and an optional 6 month open label treatment period. Patients fulfilling the enrollment criteria will be randomized to enalapril 0.625/1.25 mg (N = 30), 2.5/5 mg (N = 20) or 20/40 mg[2] (N = 50). Children < 50 kg will receive the lower dose in each group while children ≥ 50 kg will receive the higher dose. The primary endpoints are the change in siDBP from baseline to day 15 and from day 15 to the end of the randomized washout period.

The sample size was based on detecting a significant common trend at $\alpha = .05$ for a 5 mmHg difference between the extreme doses with a power = .80 (s.d. = 8 mm Hg). There is no adjustment of sample size to account for dropouts. The power calculation for the second phase does not account for dropouts in the first phase. This is unrealistic if the second phase becomes pivotal to the interpretation of the study[3]. The analysis for the treatment effect (change in siDBP from day 15 to baseline) will attempt to detect a significant non zero slope. If a zero slope cannot be excluded, the change in siDBP from day 29 to day 15 will be analyzed[4]. The sponsor submitted a new statistical analysis plan on 2/16/99 (serial no. 193).

Impression

The protocol is acceptable except for the failure to insure that a sufficient number of patients reach the randomized placebo withdrawal. There should be some assurance that there is sufficient power to detect a difference between placebo and enalapril in this phase. Because the pediatric rule for obtaining additional exclusivity does not depend on the outcome, it is important that the study provide information that is interpretable. If the first phase analysis results in a zero slope for dose response, then the second randomized withdrawal phase becomes important. The protocol as written does not account for the possibility that a large number of patients will dropout during the first phase. If this should occur, then the second phase may be underpowered to detect a difference between treatments.

Regulatory Action

The sponsor contacted the division on several occasions regarding the protocol. They were informed of our concerns[5] regarding the power of the second phase and the need to discuss this with Dr. Temple. They can, however, proceed with the conduct of the study while further internal discussions resolve this issue. This issue will need resolution before the study protocol is completely acceptable.

/S/

Charles J. Ganley, M.D.

cc: orig. to file// HFD-110 file// project manager/ ganley

HFD-710 / Hong

[1] GFR = .55 x height(cm)/serum creatinine (mg/ml)

[2] Patients randomized to the 20/40 mg group will be started at one-half the dose. On day 3, they will undergo dose titration if the initial dose is tolerated.

[3] That is, if the first phase analysis does not show a non-zero slope

[4] All enalapril patients will be combined and compared to all placebo patients.

[5] 3/11/99 Drs. J. White and L. Bell

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Medical Review

IND #[redacted]
Drug Name: enalapril
Type of Document: New Protocol
Date Received: 2/11/99
Medical Reviewer: Charles J. Ganley, M.D.

IND Volume: 134.1
Sponsor: Merck
Correspondence Date: 2/5/99
Date Completed: 2/26/99

FEB 26 1999

Protocol 168

This is an open label study to evaluate the absorption and pharmacokinetics of enalapril in children. Thirty-two children aged 1 month to < 16 years (8 per age group[1]) with hypertension will be ingest enalapril[2] for seven days. Urine and blood samples will be obtained after dosing on day one and seven. An open label follow-up period is optional.

Impression

The protocol is acceptable. Biopharm should review this protocol.

/S/

Charles J. Ganley, M.D.

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[1] Group I: 1 month to < 2 years, Group II: 2 to < 6 years, Group 3: 6 to < 12 years, Group IV: 12 to < 16 years

[2] dose is dependent on Group and weight of subject

KB

Medical Review

OCT 23 1998

#:

Drug Name: enalapril
Type of Document: pediatric proposal
Date Received: 7/30/98
Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume: 133.1
Sponsor: Merck
Correspondence Date: 7/29/98
Date Completed: 10/22/98

The sponsor submits a proposal for the study of enalapril in the pediatric hypertensive population. The program would include the following:

1. a hypertension study,
2. a post-marketing safety review,
3. literature reviews in hypertension and CHF, and
4. an epidemiology study of a case series (from chart review).

Hypertension Study (see attached summaries)

Without going into great detail, the proposed study is a randomized, double-blind, active control trial in 80 hypertensive pediatric patients. Patients would be included if their blood pressure exceeded the 95th percentile for age and gender and are 6 - 16 years of age. Subjects would be randomized to either enalapril or lisinopril. The initial dose for each is 2.5 mg and would be titrated up based on response. Patients are treated for 8 weeks.

Post-Marketing Safety Review

Merck searched their adverse event database and identified 122 adverse events reports for enalapril in pediatric patients. The individual reports are not included in this submission. A review of this information would be a worthwhile endeavor.

Literature Reviews

The sponsor has contracted with two physicians to review and summarize the published literature for enalapril and enalaprilat in hypertension and CHF.

Epidemiology Study

The sponsor proposes to perform a case series study from the records of a physician who has treated more than 100 pediatric hypertensive patients with enalapril.

Conclusion

The only information that appears to be of some value is the post-marketing safety review. A review of the adverse events database for events in the pediatric population should be a perquisite for all pediatric proposals.

The primary objective of the hypertension study is to show that siDBP is reduced with enalapril compared to baseline. Because enalapril is an effective anti-hypertensive agent, it would be a surprise if it did not achieve this goal. There is already information available to suggest that enalapril reduces blood pressure in pediatric patients. The proposed study does not provide any additional relevant information in the pediatric population.

The epidemiology study will provide some safety data but it would be difficult to extrapolate to the general population because it involves only one site.

The literature review would be interesting but not necessary. A listing of the references from the literature with selected articles provided would be just as meaningful.

Regulatory Action

The sponsor should be notified that the proposed study is inadequate. An acceptable plan for study in the pediatric hypertensive population developed at the Office level (ODEI) should be provided to the sponsor. A review of the safety database as proposed by the sponsor should be included in the development plan.

/S/

Charles J. Ganley, M.D.

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Medical Review

JUL 24 1998

NDA #: 18-998/N-000©
Drug Name: enalapril
Type of Document: Package for Pediatric Exclusivity
Date Received: 7/1/98
Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume:
Sponsor: Merck
Correspondence Date: 6/30/98
Date Completed: 7/24/98

The submission includes 1) references from the literature [1], 2) a proposed protocol for the study of enalapril in hypertensive pediatric patients. The purpose of the submission is to obtain additional exclusivity on the enalapril patent by conducting a study in pediatric patients. The protocol is a randomized, parallel dose, multi-center, double-blind, active control trial in eighty hypertensive patients 6 - 16 years of age. Patients will be randomized to enalapril (2.5 - 20 mg) or lisinopril (2.5 - 20 mg) which will be titrated to effect. The primary measure of efficacy is the change in siDBP within treatment groups at week 8.

Impression

The proposed study does not provide any meaningful information for the pediatric population. Enalapril has already been shown to lower blood pressure. It is just not clear what dose should be used in the pediatric population. This study will not answer that question. The lack of any meaningful control does not allow for an adequate assessment of individual doses.

The sponsor proposes using the tablets currently marketed. Many pediatric patients are not willing to ingest tablets and there is no provision to study lower doses than those currently available. There should be some provisions to study alternate formulations[2] and lower doses.

The proposed package does not support extension of market exclusivity.

Regulatory Action

The DCRDP and ODEI need to determine which objectives and study designs in hypertensive pediatric patients are sufficient to warrant the extension of exclusivity.

The sponsor should be informed that the package is not adequate.

/S/

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[1] ediatric Hypertension, Enalapril use in pediatric patients, epidemiology of pediatric hypertension

[2] could include specific formulations (liquid, powder) developed for the pediatric population or various ques parents could utilize to administer current formulations.