CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-998/S-059

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

REGULATORY AFFAIRS

SEP 24 1999

LARRY P. BELL, M.D

Food and Drug Administration
Rockville MD 20857

NDA 18-998

SEP 22 1999

Merck & Co., Inc.
Attention: Larry P. Bell, M.D.
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Bell:

Reference is made to your request for a Written Agreement dated May 26, 1999, and our amended Written Request dated September 8, 1999, for pediatric studies of enalapril maleate. We are issuing this Written Agreement pursuant to your request and, where noted, agreeing to specific clarifications of our amended Written Request. For ease of reference, we are providing the page number and paragraph heading in the amended Written Request letter that pertain to the agreements.

The Food and Drug Administration and Merck & Co., Inc. agree to the following:

Page 1: **Strategy**

Bullet three details the safety data to be provided. In the amended request, safety data from the controlled trial, open treatment phase or comparable database, and a summary of all available safety data in pediatric patients are to be provided.

You propose providing the safety data from the dose-ranging and PK controlled studies, a retrospective medical chart review of 80 to 100 pediatric hypertensive patients in a pediatric nephrology practice treated with enalapril to describe adverse events, effects on blood pressure, and doses used, as well as a review of all available safety information in pediatric patients from postmarketing surveillance and the literature.

We find your proposal acceptable.

Page 3: **Eligibility**

The amended Written Request asks that you take steps to obtain a reasonable distribution of age, race, and gender in the dose-ranging trial.

You propose that approximately 50% of the patients will be 6 to 12 years old (or Tanner Stage 3). As you will note from the **Recruiting** paragraph of the amended Written Request, if adolescents are included in the trial, at least 50% of the patients should be 6-12 years old or $\leq$Tanner stage 3 or younger.

You propose to include 10-30% African-American patients and 25-50% female patients.

We find this proposal acceptable, provided that no fewer patients than stipulated by the lower bound of the percentages are included. At least 50% of the patients must be 6 to 12 years or ≤ Tanner stage 3 or younger.

Format of Reports

You may submit this report with essential data in electronic form, with case report forms annotated with the names of the SAS variables used. You state that you intend to submit a report with data definition tables to allow navigation through the SAS transport files. You note that all data points entered onto the case report forms that pertain to the study will be included as a variable in the data definition tables, although some text fields considered supportive to the data are not included.

We find your proposal acceptable.

We note that you plan to submit the data on or before the date of patent expiration for enalapril maleate. Since this date will be before the date of the amended Written Request, no special agreement is needed to that which is provided by statue.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Any changes to this agreement should be made in writing by consensus under a separate correspondence. Alterations to this document without consensus are not valid.

Bonnie J. Goldmann, M.D.
Vice President, Regulatory Affairs
Merck & Co., Inc.

/S/ 9/22/99
Robert Temple, M.D.
Director, Office of Drug Evaluation I
Center for Drug Evaluation and Research

Copy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 8 1999

Two Years from
the Date of this Letter SEP 8 2001

NDA 18-998

Merck & Co., Inc.
Attention: Larry P. Bell, M.D.
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Bell:

Reference is made to your May 26, 1999 letter proposing a Written Agreement for pediatric studies of enalapril maleate.

We have reviewed your letter, and, since both general and specific issues are involved, we are issuing an amended Written Request as well as a Written Agreement. Please note that the following Written Request supercedes that of December 23, 1998, which is no longer valid.

Strategy

The requested data will provide guidance for the use of enalapril maleate to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial, and an open treatment phase following the trial or other comparable database, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of enalapril maleate on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

Pediatric Subgroups

Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1 - 24 months),
- pre-school children (age 2 - 6 years),
- school-age children (age 6 – 12 years or ≤ Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (> 12 years or > Tanner Stage 3 - 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide "children" into "pre-school "and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure a mixture of black and non-black patients.

Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailablility compared to the marketed product.

Dose-ranging Trial

Trial Design

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of enalapril maleate is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of enalapril maleate, with the doses chosen to give blood levels in a range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose.[1] After two weeks of treatment,[2] the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.[3] If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show not effect), but it would be interpretable.

---

[1] Doses would usually be derived from adult doses scaled by body surface area, but there should be, from PK data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.

[2] The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

[3] In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful.[4] In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close follow-up and withdrawal to open-label treatment at the discretion of their physicians. The analysis of Trial C would be a slope analysis for the first phase, but then (if the first phase revealed a flat dose-response curve) an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a positive dose response (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower on active treatment). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of enalapril maleate and then randomly withdrawn to lower doses (including placebo), with the same close follow-up, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must also be included, and at least 50% of the patients in the trial should be 6 – 12 years old or ≤ Tanner Stage 3 or younger. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with enalapril maleate or other therapy should be neither required nor disqualifying.

Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

---

[4] When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional (P= 0.05) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to enalapril maleate and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life, C_{max}, and t_{max} in pediatric subjects of the various age groups.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. You may submit this report with essential data in electronic form, with a case report form annotated with the names of the SAS variables used.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug product to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population[5] that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product is approved.

Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before two years from the date of this letter. Please remember that pediatric exclusivity only adds to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission

APPEARS THIS WAY
ON ORIGINAL

[5] For example, pediatric patients with hypertension secondary to advanced renal disease.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

Director
Office of Generic Drugs
HFD-600, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

We intend to issue a Written Agreement pursuant to your letter of May 26, 1999 under separate cover.

If you have any questions, please contact:

Zelda McDonald
Regulatory Heath Project Manager
(301) 594-5333

Sincerely yours,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

BONGIOVANNI

IND [redacted]

Merck Research Laboratories
Attention: Jeffery R. White, M.D.
Sumneytown Pike, P.O. Box 4
West Point, PA 19486

MAR 26 1999

Dear Dr. White:

Please refer to your investigational new drug application (IND) for enalapril maleate.

In reviewing your submissions of December 28, 1998 and February 16, 1999, serial numbers 187 and 193, our Medical Officer and Statistician have raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

/S/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure
C Ganley MOR 3/12/99 and 3/16/99
J Hung Stat Review 3/22/99

cc:
Original
~~HFD-110~~
HFD-110/K Bongiovanni
sb/3/25/99

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

K. Bongiovanni

DEC 23 1998

Two Years from
the Date of this Letter DEC 23 ...

IND [redacted]
NDA 18-998

Merck Research Laboratories
Attention: Jeffrey R. White, M.D.
Sumneytown Pike, BLA-20
West Point, PA 19486

Dear Dr. White:

Reference is made to your November 13, 1998 meeting with members of the agency requesting changes to FDA's October 24, 1998 Written Request for pediatric studies for enalapril maleate.

We have reviewed your proposed changes and are amending our Written Request. Please note that the following Written Request supercedes that of October 24, 1998, which is no longer valid.

Strategy

The requested data will provide guidance for the use of enalapril maleate to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial and an open treatment phase following the trial, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of enalapril maleate on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

Pediatric Subgroups

Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1-- 24 months),
- pre-school children (age 2-- 6 years),
- school-age children (age 6 --Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (Tanner Stage 3-- 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide "children" into "pre-school "and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
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- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure a mixture of black and non-black patients.

Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailablility compared to the marketed product.

Dose-ranging Trial

Trial Design

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of enalapril maleate is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of enalapril maleate, with the doses chosen to give blood levels in a range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose.[1] After two weeks of treatment,[2] the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.[3] If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show no effect), but it would be interpretable.

---

[1] Doses would usually be derived from adult doses scaled by body surface area, but there should be, from PK data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.

[2] The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

[3] In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful.[4] In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close followup and withdrawal to open-label treatment at the discretion of their physicians. The analysis of Trial C would be a slope analysis for the first phase, but then (if the first phase revealed a flat dose-response curve) an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a positive dose response (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower on active treatment). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of enalapril maleate and then randomly withdrawn to lower doses (including placebo), with the same close followup, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must also be included, and 50% of the patients in the trial should be Tanner Stage 3 or younger. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with enalapril maleate or other therapy should be neither required nor disqualifying.

Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

---

[4] When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional (P= 0.05) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to enalapril maleate and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life, C_{max}, and t_{max} in pediatric subjects of the various age groups.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format; or, as an alternative, you may submit an abbreviated study report along with all data in electronic form, with a case report form annotated with the names of the SAS variables used for each blank on the form.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug product to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population[5] that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product is approved.

Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before two years from the date of this letter. Please remember that pediatric exclusivity only adds to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if

[5] For example, pediatric patients with hypertension secondary to advanced renal disease.

you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

Director
Office of Generic Drugs
HFD-600, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Heath Project Manager
(301) 594-5334

Sincerely yours,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA/IND
HFD-110/division file
HFD-101/Office Director
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts
HFD-110/K Bongiovanni
sb/12/16/98;12/21/98
Initialed by: C Ganley/12/17/98
N Morgenstern/12/17/98

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND .
NDA 18-998

OCT 24 1998

Merck Research Laboratories
Attention: Jeffrey R. White, M.D.
Sumneytown Pike, BLA-20
West Point, PA 19486

Dear Dr. White:

Please refer to your proposed pediatric study request for Vasotec (enalapril maleate) Tablets, dated June 30, 1998, submitted to NDA 18-998, and the revised version dated July 29, 1998, submitted to IND 17,791.

We have completed our review of your submission and conclude that your proposed pediatric study request is inadequate.

To obtain needed pediatric information on enalapril maleate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below.

Strategy

The requested data will provide guidance for the use of enalapril maleate to reduce blood pressure in pediatric patients. These data will be derived from

a dose-ranging trial in hypertensive pediatric patients, preferably a factorial trial with at least one diuretic dose, from one of the first four pediatric age groups identified below, with possible need to evaluate the lower doses further;

pharmacokinetic trials in subjects from all of the five pediatric age groups; and

safety data, including results of controlled trials and studies to assess potential effects on growth and development in adolescents.

Pediatric Subgroups

Age groups

With respect to effectiveness, studies of antihypertensive drugs should be focused on pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide the "children" group into "pre-school"and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important, and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

To summarize, the five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1-- 24 months),
- pre-school children (age 2-- 6 years),
- school-age children (age 6 --Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (Tanner Stage 3-- 16 years).

Racial groups

Because response to therapy in adult hypertension appears to be somewhat different in black and non-black populations, your recruitment scheme should assure that your trials will include a mixture of black and non-black patients.

Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailablility compared to the marketed product.

Dose-ranging Trial

The dose-ranging trial should be a factorial, randomized, double-blind, parallel-group study comparing the antihypertensive effects of three different doses of enalapril maleate and, usually, placebo, with the doses spread out over a range from less than the lowest approved adult dose (scaled by body-surface area) to slightly more than the highest approved adult dose (again, scaled by body-surface area), both as monotherapy and added to a low dose of thiazide-type diuretic. If placebo is not used, the study will be informative, and considered an acceptable study only if a postive dose-response slope is demonstrated. If there are predicted differences in pediatric physiology that indicate that different doses should be used in the study, provide the rationale for dose selection as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. If there are pediatric pharmacokinetic data, the doses may be scaled using relative exposure data instead of body surface area calculations.

Recruiting

The trial should be performed in patients of both sexes in one of the pediatric age groups defined above, preferably school-age children. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with enalapril maleate or other therapy should be neither required nor disqualifying.

Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient

who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

Randomized-withdrawal version

Instead of randomizing entering patients to one of the four treatments, you may instead wish to force-titrate all entering patients, either newly diagnosed or previously treated, to a maximal-tolerated dose of enalapril maleate, to let them achieve steady state on this regimen, and then randomly to withdraw them to lower doses, including a placebo group, for the data-gathering portion of the trial. A risk of this design, unless previously-treated patients are withdrawn from therapy, is that treated patients' blood pressure may not return to previous hypertensive levels during the withdrawal period, decreasing the ability of the study to detect drug effects.

Endpoint

The measured endpoint should be the placebo-corrected change in blood pressure from baseline, evidence of a positive slope, or other endpoints appropriate to the study design. Depending on the group studied, the blood pressure of interest might be systolic or diastolic, reckoned in mm Hg or in percentiles from the age-specific distribution.

Statistical considerations

Dose-response trials can be analyzed to examine either the dose-response trend or group-to-group comparisons (group vs. placebo).

The trial should be designed with at least 80% power to detect a treatment effect of conventional (P= 0.05) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from each of the five pediatric age groups defined above. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a guidance document on pediatric pharmacokinetic studies will be published soon.

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to genericname and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life, C_{max}, and t_{max} in pediatric subjects of the various age groups.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug product(s) to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population* that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product(s) is/are approved.

Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before October 24, 2000. Please remember that pediatric exclusivity only adds to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request. If you would like to add marketing exclusivity to existing patent protection or to extend exclusivity that expires before October 24, 2000, please submit reports of studies responsive to this Written Request at least 30 calendar days, not including the date of expiration, before the expiration of the existing patent protection or exclusivity you would like to have considered for extension.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

---

* For example, pediatric patients with hypertension secondary to advanced renal disease.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

Sincerely yours,

/S/

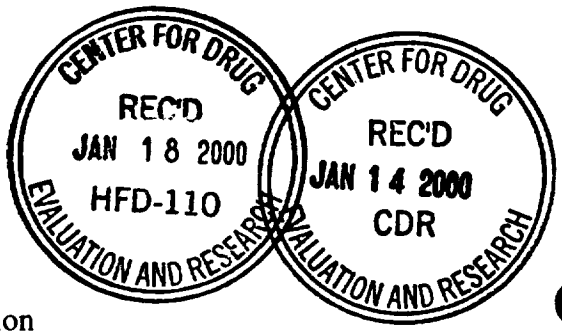
Robert Temple, M.D.
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival IND/NDA
HFD-110/division file
HFD-101/Office Director
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts
HFD-110/K Bongoivanni
sb/10/23/98
Initialed by: RLipicky/10/23/98; RTemple/10/23/98.

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

Michael C. Elia, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 3180
215 652 5000
Fax 610 397 2516



January 14, 2000

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20850

MERCK
Research Laboratories

18-998 059
SE8

NDA 18-998: VASOTEC™ (Enalapril maleate)
SUBMISSION OF PEDIATRIC STUDY REPORTS
PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED
Supplemental New Drug Application

Pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, we submit for approval a supplement to NDA 18-998. Reference is made to FDA's amended Written Request for pediatric studies on enalapril maleate dated September 8, 1999 and to the Written Agreement between FDA and Merck & Co., Inc., dated September 22, 1999. Both of these letters are enclosed as attachments to this letter.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Items 2, 3, 4, 6, 8, 10, 11, 12, 13, 16, 17, 18 and 19 of the approved New Drug Application for VASOTEC™. This sNDA describes the results of two studies recently conducted in pediatric patients: an open-label pharmacokinetic study in hypertensive infants and children aged 1 month up to 16 years, and a double-blind, dose response study in children with hypertension aged 6 to 16 years. The application also provides information on the preparation of an extemporaneous suspension formulation of enalapril for use in patients that cannot swallow tablets, and data from an open, two period, crossover study to determine the relative bioavailability of the enalapril suspension formulation and the marketed VASOTEC™ 10 mg tablets in healthy adults. Additional information on the safety of enalapril (including VASOTEC™ and VASOTEC™ I.V. Injection) use in pediatric patients is provided by a retrospective chart review of medical records of 184 pediatric patients treated at a pediatric nephrology practice, an overview of the published clinical literature, and a comprehensive evaluation of the adverse experiences in pediatric patients receiving enalapril reported in Merck's Worldwide Adverse Experience System. Based on all these data, proposed revisions to the label are included to permit the safe and effective use of VASOTEC™ in hypertensive pediatric patients.

All information is in an electronic format as indicated in the Table of Contents for this supplemental application. Review copies are also being submitted in hard copy as described in Attachment I.

With this sNDA, Merck has fulfilled the requirements described in the Written Request and our Written Agreement with FDA. Therefore, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act [Section 111 of FDA Modernization Act of 1997 (21 U.S.C. Section 355a)], we hereby request FDA attach an additional six months of marketing exclusivity to the patent protection for VASOTEC™ Tablets (enalapril maleate, U.S. Patent No. 4,374,829 listed under NDA 18-998), VASOTEC™ I.V. Injection (enalaprilat, U.S. Patent No. 4,374,829 listed under NDA 19-309) and VASERETIC™ Tablets (enalapril maleate/hydrochlorothiazide, U.S. Patent No. 4,374,829 listed under NDA 19-221). Merck reserves the right to seek a pediatric extension on any other applicable patent. Please note that Merck's U.S. Patent No. 4,374,829 has an expiration date of February 22, 2000. We understand that, in accordance with Section 505A(e) of the Federal Food, Drug and Cosmetic Act, the submission of this application less than sixty days prior to patent expiration necessitates that the Agency delay the acceptance or approval of any relevant 505(j) application or 505(b)(2) application, even if the Agency's determination occurs after February 22, 2000. In accordance with our Written Agreement and the Agency's Revised Guidance for Industry, a facsimile copy of this cover letter is being provided to the Director, Office of Generic Drugs.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This supplemental application is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing which contains the supplement. All documents requiring signatures for certification are included as paper for archival purposes.

A list of Reviewers from the Division of Cardio-Renal Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Zelda McDonald, FDA, Project Manager. MRL will follow-up with Ms. McDonald to ensure that the appropriate Reviewers have been given access to the electronic dossier.

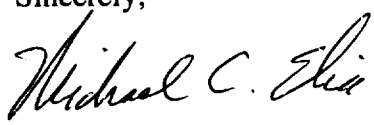
In accordance with the Food and Drug Administration Modernization Act of 1997, as indicated in the attached Form 3397, no user fee is required for this supplemental application.

Reference is made to 21 CFR Part 54, *Financial Disclosure Investigators.* Data from three clinical studies 167/169, 168/172, and 170, are presented in this application. Financial Disclosure certification and disclosure information as outlined in the regulations are provided under Item 19.

We consider the filing of this supplement to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Michael C. Elia, PhD, (610-397-3180) or, in his absence, Robert E. Silverman, MD, PhD, (610-397-2944).

Sincerely,



Michael C. Elia, PhD
Director, Regulatory Affairs

Attachment 1
Federal Express #1
Q:\baf\enal\fdalett\enalpeds_cover

cc: Ms. Zelda McDonald, FDA, Project Manager (cover letter only)
Division of Cardio-Renal Drug Products
HFD-110, Room 5024
Federal Express #2

Dr. Kenneth Edmunds, Jr. (cover letter only)
Division of Technology Support Services Staff
HFD-073, Room 8B45
Federal Express #3

Maryann Holivac (cover letter + patent)
Food And Drug Administration
HFD-090, Room 235
5516 Nicholson Lane
Rockville, MD 20895
Federal Express #4

Ms. Debra Pagano (administration and chemistry section)
Philadelphia District Office
(HFR-CE100)
Food and Drug Administration
U.S. Custom House Room 900
2nd & Chestnut Streets
Philadelphia, PA 19106-2973
Federal Express #5

Office of Generic Drugs (OGD), FDA (facsimile of cover letter)
Attn: Director, OGD (HFD-600)
(301) 594-0183

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

DUPLICATE

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 2310
215 652 5000
Fax 610 397 2516
Email: larry_bell@merck.com

October 1, 1999

MERCK
Research Laboratories

Raymond J. Lipicky, M.D. - Director
Division of Cardio-Renal Drug Products
HFD-110, Room 5039
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

SUPPL NEW CORRESP

BNC

NDA 18-998: VASOTEC™ Tablets (Enalapril Maleate)
Fully Executed Written Agreement

Dear Dr. Lipicky:

Reference is made to the above NDA, to Merck's request for a Written Agreement dated May 26, 1999, and to the revised Written Request for enalapril pediatric studies dated December 8, 1999. Reference is also made to the two original copies that were received from the Agency of the final Written Agreement, dated September 22, 1999, signed by Robert Temple, MD (FDA). One original, signed by Bonnie Goldmann, MD (MRL), is enclosed.

If you have any questions or need additional information, please contact Larry P. Bell, MD, (610-397-2310) or, in my absence, to Bonnie J. Goldmann, MD (610-397-2383).

Sincerely,

Larry P Bell

Larry P. Bell, MD
Senior Director, Regulatory Affairs

Enclosure
Federal Express #1

Desk Copy w/Enclosure: Ms. Zelda McDonald, WOC2, HFD-110, Room 5024
Federal Express #2

Jeffery R. White, M.D.
Director
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 3180
215 652 5000
Fax 610 397 2516
Email jeffery_white@merck.com

May 26, 1999

MERCK
Research Laboratories

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

SUPPL NEW CORRESP
SNC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 27 1999
HFD-110

NDA 18-902 VASOTEC® (Enalapril Maleate)

Proposed Pediatric Written Agreement

Dear Dr. Lipicky:

Reference is made to the Agency's Written Request for pediatric enalapril hypertension studies dated December 23, 1998, to Section 111 of the Food and Drug Administration Modernization Act, and to a meeting between the FDA and Merck Research Laboratories (MRL) on November 13, 1998. This submission details Merck's plans for fulfilling the Agency's Written Request for enalapril pediatric studies. To this end, the FDA and Merck agree to the following terms:

Pediatric Dose-Ranging Study

Merck will conduct a double-blind, randomized, multicenter, dose response study of enalapril in children with hypertension. The study will enroll at least 100 hypertensive children, aged 6 to16 years. Following a 2-7 day washout period, patients will be enrolled in a 14-day active controlled, dose response study with doses of enalapril ranging from 0.625-40 mg/day. A 14-day randomized withdrawal to placebo will follow the initial 14 days of active therapy. At least 100 patients will complete the study to ensure adequate statistical power.

The primary objective of this study is to define the dose response relationship for enalapril in children with hypertension after a 14-day double-blind active treatment period. The study will also investigate the safety and tolerability of enalapril in a dose range from 0.625-40 mg/day. In addition, the mean change in blood pressure during the 14-day double-blind randomized washout period will be defined.

The overall study will be race, gender, and age-balanced (via central monitoring at Merck) with approximately 10 to 30% African-American patients (race will be determined by patient self-proclamation), approximately 25 to 50% female patients, and approximately 50% patients aged 6 to 12 years (or Tanner Stage 3).

Patients from the dose response study may be enrolled in an optional six-month open label extension period. Data on serious adverse experiences which are reported to MRL prior to the data collection cutoff date will be summarized in the filing.

Pharmacokinetic Study

An open-label study to investigate the pharmacokinetics of enalapril in hypertensive children and infants will be conducted. The study will enroll a total of 32 hypertensive children, divided into four age groups. The groups are defined as follows:

aged 1 month to < 2 years;
aged 2 to < 6 years;
aged 6 to < 12 years; and
aged 12 to < 16 years

The study will determine first dose and steady state typical serum PK parameters (AUC, Tmax and Cmax) of enalapril and enalaprilat. In addition, urinary recovery of total and free enalaprilat will be estimated. Finally, the safety and tolerability of enalapril in patients age 1 month to less than 16 years of age will be investigated.

An optional 6-month open-label extension study will be conducted on these patients. Serious adverse experiences that are submitted to MRL prior to the data cutoff date will be summarized and included in the filing.

Relative Bioavailability Study

Since the younger patients in the pharmacokinetic study described above will be unable to swallow tablets, an enalapril suspension will be used to deliver enalapril to those patients who cannot swallow tablets. The purpose of this study is to compare the bioavailability of marketed enalapril tablets to the bioavailability of the oral enalapril suspension used in the youngest patients in the pharmacokinetic study.

This relative bioavailability study will enroll 16 normal volunteers in a two-period crossover single dose study. The primary objective of the study is to compare the relative bioavailability of enalapril suspension, 10 mg vs. the 10 mg marketed enalapril tablet. In addition, the serum concentration profile of enalapril and enalaprilat following administration of enalapril suspension 10 mg and 10 mg marketed enalapril tablet will be determined. This study will measure typical serum PK parameters (AUC, Tmax and Cmax) as well as urinary drug levels.

Safety Information

Safety information will be obtained from the studies described above. Serious adverse experiences from the optional open label extension pediatric hypertension studies that are reported to MRL prior to the data collection cutoff date will also be included in this filing. In addition, MRL will review pediatric safety information for enalapril from the Merck Worldwide Adverse Experience System and provide a summary of this review in the filing.

Enalapril Pediatric Experience Study

MRL will also conduct a retrospective medical chart review, consisting of approximately 100 pediatric hypertensive patients. The primary objectives of this retrospective study are as follows:

1. to describe the adverse events that occur over time with the use of enalapril in a hypertensive, pediatric cohort in a referral clinical center;

2. to describe the effect of enalapril on blood pressure at initiation of therapy and during maintenance of blood pressure control in this pediatric cohort;

3. to describe the use of enalapril (effect on blood pressure and adverse events) in different subcategories of pediatric hypertension (e.g. renovascular hypertension, renal parenchymal hypertension and primary hypertension);

4. to describe the average dose and the range of doses of enalapril overall and by age group.

A synopsis of this medical chart review study is attached.

Review of Literature

MRL will provide, at the time of filing, a manuscript summarizing the available published literature on the use of enalapril in pediatric patients.

Labeling Changes

MRL will propose labeling changes to describe study results and to provide instructions for preparation of the enalapril suspension used in these clinical studies.

Submission of Results

As discussed in the November 13, 1998 meeting, MRL intends to submit abbreviated study reports in lieu of full study reports of the clinical studies described above. MRL intends to submit abbreviated clinical study reports and the other materials described above in a Supplemental New Drug Application on or before the date of VASOTEC® patent expiration. MRL understands that the additional period of marketing exclusivity provided for under Section 111 of the Food and Drug Administration Modernization Act will also extend marketing exclusivity for other Merck products containing the enalapril active moiety. Thus, MRL anticipates that the period of marketing exclusivity for NDA 18-998: VASOTEC® Tablets, NDA 19-309: VASOTEC® I.V. Injection, and NDA 19-221: VASERETIC® Tablets will be extended upon successful completion and submission of the program described above.

If you have questions or need additional information, please contact Jeffery R. White, M.D., (610-397-3180) or, in my absence, to Larry P. Bell, M.D. (610-397-2310).

Sincerely,

Jeffery R. White, M.D.
Director
Regulatory Affairs

Attachments

Redacted 18

pages of trade

secret and/or

confidential

commercial

information

Jeffery R. White, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 3180
215 652 5000
Email jeffery_white@merck.com

DESK COPY

March 31, 1999

MERCK
Research Laboratories

Raymond J. Lipicky, M.D. - Director
Division of Cardio-Renal Drug Products
WOC2, HFD-110, Room 5002
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Serial No. 198

IND [redacted] MK-0421 (Enalapril Maleate)
Response to FDA Request For Information

Dear Dr. Lipicky:

Reference is made to the above IND, CMC submissions to this IND (January 12, 1999, Serial No. 188; January 18, 1999, Serial No. 189; January 22, 1999, Serial No. 190); to two facsimiles received from the Agency on March 8 and March 9, 1999, and to the teleconference held March 10, 1999 between Dr. Stuart Zimmerman (FDA) and Dr. Jeffery White, Dr. Thomas DiFeo, and Mr. William Creveling (MRL). The teleconference was held to respond to the chemistry reviewer's questions regarding supplies for the enalapril pediatric hypertension study. Reference is also made to a telephone conversation between Drs. Zimmerman and White on March 19, 1999, in which additional chemistry questions were presented.

With this submission, we are summarizing commitments made by MRL in the March 10, 1999 teleconference and are providing responses to the questions posed by Dr. Zimmerman in the March 19, 1999 telephone conversation.

Questions concerning this information should be directed to Jeffery R. White, M.D. (610-397-3180) or, in my absence, to Larry P. Bell, M.D. (610-397-2310).

Sincerely,

for Jeffery R. White, M.D.
Director, Regulatory Affairs

CENTER FOR DRUG
REC'D
APR - 1 1999
HFD-110
EVALUATION AND RESEARCH

Attachment

Federal Express #1

Desk Copies w/Attachment:
Ms. Kathleen Bongiovanni – WOC2, HFD-110, Room 5023 – Federal Express #1
Via Facsimile to Dr. Stuart Zimmerman, WOC2, HFD-110, Room 5080 – Confirmation Copy Federal Express #1

Redacted 3

pages of trade secret and/or confidential commercial information

R/S# (1)

MERCK
Research Laboratories

TELECOPIER MESSAGE

MERCK RESEARCH LABORATORIES
REGULATORY AFFAIRS - DOMESTIC
FIVE SENTRY PARKWAY EAST, BLUE BELL, PA 19422

TO: Dr. Stuart Zimmerman
LOCATION: FDA, HFD-110, Rm 5080
PHONE: (301) 594-5350
FAX: (301) 594-5494/95

FROM: Jeffery R. White, M.D.
LOCATION: BL A-20
DATE: 3/10/98
PHONE: 610/397-3180
FAX: 610/397-2516
PAGES including cover sheet: 11

Special Comments:

Information for the 2 PM teleconference today. We will place the call to you.

CONFIDENTIALITY NOTE: This fax contains confidential information belonging to Merck & Co., Inc. If you are not the intended recipient, any disclosure, copying of use of this fax is strictly prohibited, and you should immediately notify the sender to arrange for return of the documents.

MERCK
Manufacturing Division

MEMO

REGULATORY & ANALYTICAL SCIENCES - CHEMISTRY, MANUFACTURING, AND CONTROL

DATE: March 09, 1999

TO: Jeffery White **LOC:** BLA-20

FROM: Alison Thomas-Steele **LOC:** WP20-106

SUBJECT: **IND [redacted] Informational Amendment - Chemistry, Manufacturing and Controls (Enalapril Pediatric Study) - Response to FDA Reviewer Questions:**
(a) Tablets Composition: Clinical Supplies vs. NDA formulations
(b) [redacted] Test Results

The following information regarding formulated materials to be used in the Enalapril Maleate Pediatric Clinical Study is supplied as additional information in response to questions from the FDA reviewer.

1. The qualitative and quantitative composition of the clinical tablets supplies is provided which compares the clinical formulation to the formulation filed in the NDA.

2. A copy of the [redacted] Test results from [redacted] is contained in Attachment 1. A copy of the GMP statement letter provided in the January 12, 1999 IND amendment is also supplied herein (Attachment 2) for ease of review.

This document has been [redacted] and is suitable for submission. Please do not hesitate to contact me if you should have questions.

Best regards,

Redacted 8

pages of trade secret and/or confidential commercial information

(11)

Merck Research Laboratories
Enalapril Maleate IND [redacted]
Information Amendment: Chemistry, Manufacturing and Control (Pediatric Indication Study)
Response to FDA Reviewer Questions

December 21, 1998

Ms. Alison Thomas-Steele
Merck & Co., Inc.
P.O. Box 4
West Point, PA 19486

Dear Ms. Thomas-Steele:

This letter is to certify that the facilities, equipment, procedures, records, and methods used by [redacted] in the testing of pharmaceutical raw materials, components, drug substances, and finished drug products are in compliance with 21CFR§210 and 21CFR§211 (current Good Manufacturing Practices). We are an FDA registered contract analytical laboratory. Our registration number is [redacted]

If there are any questions, or additional information is required, please contact me at [redacted] or contact your client service representative.

Sincerely,

/S/

Quality Assurance Officer

K.T

MAR - 9 1999

Facsimile Transmittal

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it by mail to DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857.

Transmitted to FAX number: 610-397-2516

Attention: Jeffy White

Company name: Merck

Phone: 610-397-3180

Subject: IND [redacted] (SN 187-188)*

Date: 3/9/99

Pages including this sheet: 2

From: Stuart Zimmerman, Ph.D
Phone: (301) 594-5350
FAX: (301) 594-5494

*More CMC questions - follow-up (see attached)

/S/
Signature

cc: IND [redacted] ORIG.
HFD-110 / DOC. FILE
HFD-110/CSO
HFD-110 / Zimmerman

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pages of trade secret and/or confidential commercial information

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MAR - 8 1993

Facsimile Transmittal

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

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Pages including this sheet: 2

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*Questions mentioned by phone - follow-up message - see attached

Stuart Zimmerman
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