

HFD-1041 Murphy

NDA 20-632

JUN 17 1999

Knoll Pharmaceutical Company
Attention: Robert J. Mandetta
Associate Director, Regulatory Affairs
3000 Continental Drive, North
Mount Olive, NJ 07828 1234

Dear Mr. Mandetta:

Reference is made to your Proposed Pediatric Study Request submitted on January 29, 1999 for Meridia (sibutramine hydrochloride monohydrate) Capsules to NDA 20-632.

To obtain needed pediatric information on sibutramine hydrochloride monohydrate capsules, 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 following study:

Type of study:

A one-year study of efficacy and safety in obese male and female adolescents.

Objective/Rationale:

To compare the effectiveness of behavior therapy plus exercise plus placebo to behavior therapy plus exercise plus sibutramine in reducing weight in obese adolescents. To assess the safety of sibutramine in a population of obese adolescents.

To assess the steady-state pharmacokinetics of sibutramine and its active metabolites in 12 to 16 year old obese adolescents.

Indication to be studied:

Treatment of obese adolescents who have a body mass index of 34 kg/m^2 – 44 kg/m^2 .

Study design:

A multicenter, randomized, double-blind, placebo-controlled, dose-escalation study. Insofar as possible, subjects should be recruited from all major regions of the United States.

A steady-state pharmacokinetic study at the three study doses should be conducted in 12 to 16 year old obese male and female adolescents. This study can be conducted as an appropriate subset(s) of a clinical study using sparse sampling, or as a conventional pharmacokinetic study.

Age group in which studies will be performed:

Ages 12-16 years.

Number of patients to be studied:

A total of 300 subjects randomized to sibutramine treatment. The study population should be comprised of 50-75% females and at least 30% African-American heritage.

Entry criteria:

Male and female subjects age 12-16 years, with no major medical or psychiatric conditions.

Clinical endpoints:

Change from baseline in weight, height, body mass index, growth, blood pressure and pulse, fasting glucose, insulin and lipids.

Study evaluations:

Report of 24-hour ambulatory blood pressure and pulse data during at least a one-week period at a dose of 15 mg per day. These data should be from a random subset of at least 15 sibutramine- and 15 placebo- treated subjects.

Report of physical examination of the cardiovascular system at each study visit.

Report of echocardiographic data (i.e., valve function, left ventricular thickness) from a random sample of at least 30 sibutramine- and 15 placebo-treated subjects. These data should be collected at baseline and at the completion of the one-year study.

Report of changes in body composition as assessed by DEXA in a random subset of at least 15 placebo- and 15 sibutramine-treated subjects.

Report of effects of sibutramine on cognitive function (i.e., learning, memory, and psychometrics) in all of sibutramine- and all of placebo-treated patients.

Relevant pharmacokinetic parameters for sibutramine and its active metabolites should be calculated. Tanner stages for the patients in the pharmacokinetic study must be recorded and provided in the study report. Additional information related to pharmacokinetic studies can be found in the Population Pharmacokinetic guidance [www.fda.gov/cder/guidance/1852fnl.pdf]

and in the draft guidance document on pediatric pharmacokinetic studies [www.fda.gov/cder/guidance/1970dft.pdf].

Drug information:

- ***Dosage form:*** capsules
- ***Route of administration:*** oral
- ***Regimen:*** 5, 10, and 15 mg once daily or matching placebo
- ***Formulation:*** same as marketed

Drug Specific Safety Concerns:

Primarily, the effects of sibutramine on blood pressure and pulse. An algorithm should be used to monitor and follow blood pressure and pulse.

Statistical information, including:

The evaluation of primary and secondary parameters using a two-factor ANOVA, with explanatory variables of treatment and gender. The primary analysis population is the set of all randomized subjects.

Labeling that may result from the study:

Addition of information summarizing the safety and efficacy and pharmacokinetic information derived from these trials. Addition of pediatric dosing information to the DOSAGE AND ADMINISTRATION section.

Format of report to be submitted: full study reports or analyses not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Complete study report with accompanying computer-based clinical and safety data listings.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before December 31, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the 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. We recommend that you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*), with FDA before developing pediatric protocols. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed

written agreement. 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.

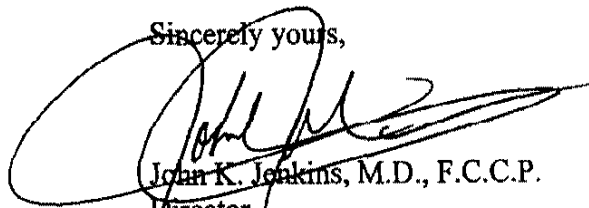
If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large 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 look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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 in the pediatric population.

If you have any questions, please contact Maureen Hess, MPH, RD, Consumer Safety Officer, at (301) 827-6411.

Sincerely yours,



John K. Jenkins, M.D., F.C.C.P.

Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:

NDA 20-632

(b) (4)

HFD-510/Div.File (2)

HFD-510/EColman/GTroendle/JTemeck/MHess/EGalliers/HAhn/TSahlroot

HFD-102/JJenkins/LRipper

HFD-870/HAhn/JWei

HFD-715/TSahlroot

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-104/VKao

Draft: 4.2.99

Final: 5.13.99

Concurrence:

EColman/5.13.99/GTroendle/5.13.99/EGalliers/5.17.99/TSahlroot/5.17.99/JTemeck/5.14.99/

HAhn/5.17.99/SSobel/5.17.99/

PEDIATRIC WRITTEN REQUEST LETTER

INFORMATION REQUEST (IR)



Handwritten signature and date: 5/27/99