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NDA 20-764

Glaxo Wellcome
Attention: Elizabeth A. McConnell, Pharm.D.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

DEC 17 1998

Dear Dr. McConnell:

Reference is made to your Proposed Pediatric Study Request submitted on August 3, 1998 to NDA 20-764 for Lamictal (lamotrigine) Chewable Dispersible Tablets.

To obtain needed pediatric information on lamotrigine, 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:

Types of studies:
Study 1: Pediatric Efficacy and Safety Study
Study 2: Pediatric Safety Study
Study 3: Pharmacokinetic Study

Objective/rationale:
Study 1: To establish the efficacy and short-term safety of lamotrigine as add-on therapy in the treatment of pediatric patients 1 month to 16 years of age with partial seizures.

Study 2: To determine the long-term safety of lamotrigine as add-on therapy in the treatment of pediatric patients 1 month to 2 years of age with partial seizures.

Study 3: To determine the pharmacokinetics of lamotrigine in pediatric subjects 1 month to 10 months of age.

Indication(s) to be studied:
Adjunctive therapy in the treatment of partial seizures in pediatric patients 1 month to 16 years of age with partial seizures.

Study design:
Study 1: Double-blind, randomized, parallel group comparison, of at least 3 months duration, of lamotrigine versus placebo as add on therapy in pediatric patients 1 month to 16 years of age with partial seizures.

Study design (continued):
Study 2: Open, uncontrolled, long-term treatment of pediatric patients 1 month to 2 years of age with partial seizures.

Study 3: Single dose or multiple dose study of lamotrigine in appropriate pediatric subjects 1 month to 10 months of age.

Age group in which studies will be performed: Study 1 should include subjects 1 month to 16 years of age. Study 2 should include subjects 1 month to 2 years of age. Study 3 should be appropriately designed and analyzed to determine age-dependent pharmacokinetics of age group 1 month - 10 months.

Number of patients to be studied or power of study to be achieved:
Study 1: A sufficient number of pediatric patients to be able to detect a statistically significant difference between treatment and control on a valid measure of seizure frequency.

Study 2: A sufficient number of pediatric patients to adequately characterize the safety of lamotrigine at clinically effective doses for a sufficient duration.

Study 3: A sufficient number of completed subjects to adequately characterize the pharmacokinetics of age group 1 month - 10 months.

Clinical endpoints:
Study 1: A single standard measure of seizure frequency should be chosen as the primary outcome measure, and standard measures of safety (clinical-including signs and symptoms- and laboratory).

Study 2: Appropriately frequent standard measures of safety (clinical-including signs and symptoms- and laboratory)

Study 3: Pharmacokinetic measurements as appropriate.

Study evaluations:
Study 1: Safety and effectiveness data for a duration of at least 3 months.
Study 2: Safety data as discussed above.
Study 3: Reports of relevant pharmacokinetic parameters.
Drug information:
Dosage form: oral tablet and other formulation as appropriate for younger patients
Route of administration: oral and other as appropriate
Regimen: To be determined by the development program
Formulation: solid oral dosage form and other formulation as appropriate for younger patients

Safety concerns: Serious rash, acute multiorgan failure (with or without disseminated intravascular coagulation), hypersensitivity, pure red cell aplasia.

Statistical information, including:
Study 1: Assessment of the between group difference, stratified by age, on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated.

Study 2: Descriptive analysis of the safety data.

Study 3: Descriptive analysis of the pharmacokinetic parameters.

(b) (4)

Format of reports 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. Include other information as appropriate.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before August 24, 2003, to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity only extends 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 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 as **"PROPOSED CHANGES IN 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, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at 301-594-5793.

Sincerely yours,

Robert Temple 12/17/98

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

cc:
Archival NDA 20-764
HFD-120/division file
HFD-120/Ware
HFD-120/Leber/Katz/Feeney
HFD-100/Temple
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts

Drafted by: JHW
Initialed by:
Final:
filename: C:\My Documents\WPFILES\jwndas\N20764\wrletter.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION