



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD-104 Kao

NDA 18-644
NDA 20-358
NDA 20-711

Food and Drug Administration
Rockville MD 20857

JUL 21 2000

Glaxo Wellcome Inc.
P. O. Box 13398
Research Triangle Park, North Carolina 27709

Attention: James E. Murray
Director, Regulatory Affairs

Dear Mr. Murray:

Please refer to your new drug applications for Wellbutrin (bupropion hydrochloride) immediate-release tablets (NDA 18-644, approved for depression) and sustained-release tablets (NDA 20-358, approved for depression), and Zyban sustained-release tablets (NDA 20-711, approved for smoking cessation).

To obtain needed pediatric information on bupropion, 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 trials in pediatric patients with depression and for the indication of smoking cessation.

DEPRESSION

Background Comments on Pediatric Depression

Under current regulations [21 CFR 201.57(f)(9)(iv)], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well-controlled studies in adults for the same entity if it were believed that depression was essentially the same disease in adults and children. Under section 115 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. Unfortunately, in our view, there is little reason to assume continuity between adult and pediatric depression and our concern about the extrapolability of adult depression data to pediatric depression is more than theoretical. While we, of course, acknowledge the one published positive report of fluoxetine in pediatric depression (Emslie, et al, 1997), we are concerned about the preponderance of

negative studies of antidepressants in pediatric populations. We recognize that all of these negative studies utilized tricyclic antidepressants, and that, in addition, there are other possible explanations for the negative outcomes, e.g., sample size, entry criteria, outcome measures, etc. Nevertheless, these negative trials (at least 12 in number) lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, we believe that a pediatric depression claim for any antidepressant already approved in adult depression would need to be supported by two independent, adequate and well-controlled clinical trials in pediatric depression. In addition, a pediatric depression program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric depression, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

Background Comments on Pediatric Smoking Cessation

As is the case for depression, the Agency finds that it is not possible to extrapolate efficacy data on smoking cessation in adults to support an indication of smoking cessation in the pediatric population. Studies have demonstrated that non-pharmacologic smoking cessation methods that are effective in adults are not effective in children. Furthermore, pharmacologic treatments are aimed at addiction to cigarettes, and there is little information on the appropriate identification of addiction in pediatric smokers, who are believed to smoke for a variety of reasons other than addiction. Accordingly, we believe that efficacy data are needed to support a smoking cessation indication in the pediatric population. However, as we feel that the main task of the development program for smoking cessation in children is to develop a method of identifying pediatric patients who have the same disorder seen in adults (tobacco addiction), we believe that a single efficacy study along with confirmatory evidence from other sources, such as adult efficacy data, would suffice.

In addition, a pediatric smoking cessation program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric smoking cessation, we consider the relevant age groups to include pre-adolescents and adolescents (ages 10 through 17).

Specific Study Requirements for Each Indication

The specific requirements for each indication are described below. A single safety and pharmacokinetic database would be acceptable if relevant doses were used to cover both indications.

Specific Study Requirements for Development Program in Pediatric Depression

Types of Studies

Pediatric Efficacy and Safety Studies

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program is to establish the safety and efficacy of the study drug in the treatment of pediatric depression, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Studies

- For the controlled efficacy studies, conduct two randomized, double-blind, parallel-group, placebo-controlled acute treatment trials, with a recommended duration of at least 6 to 8 weeks. We recommend that at least one of the two studies should be a fixed-dose study including two or more fixed doses of the study drug. You may consider dosing patients on the basis of patient weight. Randomization must be stratified by the two age groups studied. Ideally, a relapse-prevention trial would follow from the acute treatment trials, involving the randomization of responders from the acute treatment trials to continuation on either study drug or placebo, with follow-up observation for relapse for a period of 6 months or more. Please note that a relapse-prevention trial is not required under this written request.

Pediatric Pharmacokinetic Study

- A pharmacokinetic study to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies or, alternatively, from population kinetic approaches applied to controlled efficacy trials or to other safety trials. A guidance document on population pharmacokinetic studies is available through the FDA website at www.fda.gov/cder/guidance/1852fnl.pdf.

Pediatric Safety Study

- Safety data should be collected in the controlled efficacy trials. Longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies.

Age Group in Which Study(ies) will be Performed – All Studies

Both children (ages 7 - 11) and adolescents (ages 12 - 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these strata.

Number of Patients to be Studied or Power of Study to be Achieved

Pediatric Efficacy and Safety Studies

- While it is difficult to specify the sample size needed to show a difference between drug and placebo in this population, it should be noted that, in the only published positive antidepressant trial in pediatric depression (Emslie, et al, 1997), there were 48 patients in each of the two treatment arms.

Pediatric Pharmacokinetic Study

- A sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of bupropion at clinically effective doses for a sufficient duration.

Entry Criteria

The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder.

Study Endpoints

Pediatric Efficacy and Safety Studies

- It is essential to identify a single primary outcome for the controlled efficacy trials, and ordinarily this should be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

Pediatric Pharmacokinetic Study

- Pharmacokinetic measurements as appropriate.

Pediatric Safety Study

- Appropriately frequent standard measures of safety (clinical - including signs and symptoms and laboratory tests).

Statistical Information

Pediatric Efficacy and Safety Studies

- These trials should have a detailed statistical plan. Ordinarily these trials should be designed with at least 80% statistical power to detect a treatment effect of conventional ($p=0.05$) statistical significance.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

Study Evaluations

Pediatric Efficacy and Safety Studies

- A scale specific to pediatric depression and sensitive to the effects of drug treatment of pediatric depression, e.g., the Children's Depression Rating Scale—Revised, and a global measure, e.g., the Clinical Global Impression (CGI).

Pediatric Pharmacokinetic Study

- The pharmacokinetic assessments should be made with respect to the study drug 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 pharmacokinetic parameters including AUC, half-life, C_{max} , t_{max} , and apparent oral clearance in pediatric subjects in the relevant age range. A draft guidance

document on pediatric pharmacokinetic studies is available at www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft).

Pediatric Safety Study

- Routine safety assessments should include vital signs, weight, clinical laboratory tests, ECGs, and monitoring for adverse events. Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate antidepressant activity.

SMOKING CESSATION

Specific Study Requirements for Development Program in Smoking Cessation

Study 1: Pharmacokinetics and Safety

- **Objective/Rationale:**
To determine the multiple-dose pharmacokinetics of bupropion and its metabolites following administration of sustained-release (SR) tablets in pediatric patients. This study should be used to aid in selection of doses for efficacy and safety evaluations in adolescent smokers. To determine the adverse event profile of bupropion in adolescent patients and to determine whether there is any age group (or weight group) for whom bupropion is so poorly tolerated that its utility as an aid to smoking cessation treatment should not be evaluated in that group.
- **Study Design:**
Multiple-dose (steady-state) pharmacokinetic study of bupropion SR tablets in three doses, including the dose recommended for smoking cessation in adults and two lower doses that may be more appropriate for smaller patients. We recommend that you identify a maximum allowable dose per kilogram body weight. Subjects may be randomized to any dose that does not exceed the maximum based on the subject's body weight.

An adequate number of blood samples should be taken at appropriate times to determine the pharmacokinetics of bupropion SR tablets and its metabolites.
- **Study Endpoints:**
Determination of plasma concentrations of bupropion, hydroxybupropion, and threo- and erythrohydrobupropion, and adverse event profile.
- **Inclusion/Exclusion Criteria:**
Male and female patients ages 10-17 years (with a reasonable distribution across this age range). If desired, these patients may also participate in a pilot trial of smoking cessation treatment.

- **Number of Patients to be Studied:**
A minimum of 18 pediatric patients, 6 patients per treatment group, should be studied to adequately characterize the multiple-dose pharmacokinetics of bupropion SR tablets at the three doses chosen.
- **Analysis of the Data to be Performed:**
Descriptive analysis of pharmacokinetic parameters of bupropion, hydroxybupropion, and threo- and erythrohydrobupropion appropriate for multiple dosing (including C_{max} , C_{min} , t_{max} , $t_{1/2}$, AUC, and accumulation index). Assessment of dose-proportionality between the doses tested. Comparison of the results obtained in adolescents in this study with historical results obtained from adults.

Study 2: Dose Ranging Efficacy/ Safety

- **Objective/Rationale:**
The objectives of this trial are to establish that bupropion hydrochloride as part of an overall smoking cessation program is effective in achieving and maintaining smoking cessation for one month in tobacco-addicted youth; to determine a safe and effective dose; and to document the ability of treating physicians to select appropriate patients. You will need to develop a means for determining reliable criteria for appropriate patient selection of tobacco-addicted youth so that young smokers who are not addicted will not be recruited, and so that labeling can convey these criteria to physicians who may wish to use the drug in adolescents. A survey to determine the knowledge, attitudes, and practices of treating physicians with respect to smoking cessation may be helpful to you in designing these criteria. You will also need to develop or identify an age-appropriate behavior modification program to be included in these studies. Because bupropion SR is intended to be used as part of a comprehensive treatment program, an overall smoking cessation program designed to effectively motivate adolescent smokers to remain cigarette-free should be an integral component of the clinical trial design.
- **Study Design:**
The trial should be a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study. Treatment duration should be 7 weeks, with one week of medication prior to quit day and six weeks of treatment during the quit attempt. Subjects should be followed off medication for an additional three months following the end of the treatment phase. Doses should include the dose recommended for adults and at least one dose that is lower. We recommend that you identify a maximum allowable dose per kilogram body weight. Subjects may be randomized to any dose that does not exceed the maximum based on the subject's body weight.

- **Clinical Endpoints:**

- **Efficacy:**

The primary outcome measure should be abstinence from smoking for a period of four consecutive weeks, based on weekly self-reporting of smoking and assessment of objective biochemical markers during the last four weeks of treatment (end of week 3 through end of week 7), using meaningful, validated markers of pediatric cigarette smoking that can be demonstrated as sensitive and reliable indicators of tobacco use.

- **Safety:**

The key safety issue is the adverse event profile in young smokers, particularly in lower weight subjects who may be at greater risk for toxicity. Patients should be queried at appropriate intervals about adverse events during treatment and monthly during follow-up, and should be followed to the resolution of any treatment-emergent events. Any adverse events that occur during treatment or follow-up should be recorded and transmitted as part of the study report. The circumstances of any deaths, discontinuations, serious adverse events, seizures, or allergic reactions requiring urgent intervention should be adequately documented and transmitted within the study report.

All other relevant safety information that is available, including an analysis and summary of postmarketing experience, should also be submitted with the study report, but is not required as part of this written request.

- **Inclusion/Exclusion Criteria:**

Cigarette smokers desiring to quit, who meet the selection criteria for tobacco addiction and who have no contraindication to the use of bupropion should be included. Patients should be recruited from age groups 10-17, unless the results of Study 1 reveal that bupropion is so poorly tolerated in younger subjects that its use should not be explored. In that case, patients should be recruited from the age group that appears to tolerate the medication.

- **Number of Patients to be Studied:**

Sufficient patients should be enrolled to detect a 20 percent attributable rate of smoking cessation between any two groups with power 0.8 and significance level 0.05 (two-sided).

- **Statistical Analysis of the Data to be Performed:**

Chi-square analysis of successful 4-week abstainers in treatment versus placebo groups. Descriptive analyses of adverse events. Analysis of response by dose per kilogram body weight.

ISSUES RELEVANT TO BOTH INDICATIONS

Drug Information

Use age-appropriate formulations in the studies described above. Since the pediatric patient population consists of both children (ages 7 - 11) and adolescents (ages 12 - 17), your marketed solid dosage formulation should be adequate for these studies.

Drug-Specific Safety Concerns

Although no concerns specifically related to administration of bupropion to pediatric patients were identified while studying bupropion in adults, nor have specific concerns been identified during the postmarketing experience, general safety issues noted in adults are also of concern in children. The key safety issue is the adverse event profile in the pediatric population, particularly in lower-weight subjects who may be at greater risk for toxicity. *In particular, the dose-dependent risk of seizure is a concern, as well as the occurrence of allergic reactions requiring urgent intervention.*

Labeling That May Result from the Studies

Changes to the Pharmacodynamics, Clinical Trials, and Indications and Usage sections; and other sections as appropriate depending on the outcome of the study.

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 Study(ies)

Reports of the above studies must be submitted to the Agency by February 28, 2004, to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended 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. 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 NDAs 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.

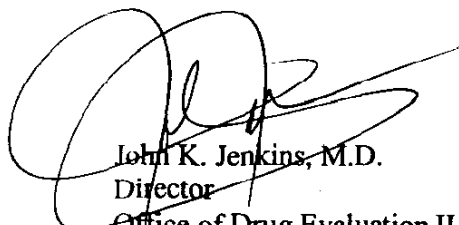
If you have any questions, call Paul A. David, Regulatory Project Manager (HFD-120), at (301) 594-5530, or Judit Milstein, Regulatory Project Manager (HFD-170), at (301) 827-7440.

Sincerely yours,



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

Sincerely yours,



John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Bupropion HCl Pediatric Written Request
Page 10

cc:

Archival NDA 18-644(HFD-120)
Archival NDA 20-358(HFD-120)
Archival NDA 20-711(HFD-170)
IND 45,794 (HFD-170-smoking cessation)
IND 13,845 (HFD-120-depression)
IND 28,676 (HFD-120-depression)
HFD-120/Div
HFD-170/Div
HFD-101/RTemple
HFD-102/Jenkins
HFD-102/Rarick
HFD-102/Ripper
HFD-120/PDavid *P 7-11-00* *WZ 7-11-00*
HFD-120/RKatz/TLaughren/AMosholder/RGlass/Gdubitsky/Andreason 2-11-2000
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy/VKao/TCrescenzi
HFD-170/McCormick
HFD-170/Milstein/Schumaker
HFD-170/Winchell 2-10-2000
HFD-170/Uppoor/Chen 2-11-2000
HFD-170/Jean/Geyer 2-23-2000
HFD-170/T. Permutt 2-10-2000

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Revised: JM 3-7-2000, 5-23-00, 6-9-00, 6-8-00, 6-22-00, 6-29-00

Rev: C. Winchell/HFD-170/2-1-00, 2-10-00, J.Jenkins 3-1-00, C. Winchell 5-23-00,
R.Uppoor 5-25-00, C. McCormick 5-24-00, C. Schumaker 5-24-00, L.Ripper 6-2-00, J.
Jenkins 6-7-00, R. Uppoor 6-22-00, I. Ripper 6-23-00, J. Jenkins 6-26-00

Revised per L. Ripper/7-5-00

Final: 7/11/00pd

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**PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)**