CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022497Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022497 **COMPLETE RESPONSE**

Cary Pharmaceuticals, Inc.
Attention: Douglas D. Cary
President and C.E.O.
9903 Windy Hollow Road
Great Falls, VA 22066 - 3550

Dear Mr. Cary:

Please refer to your new drug application (NDA) dated March 31, 2009, received April 6, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Forfivo XL (bupropion hydrochloride) extended release 450 mg tablets.

We acknowledge receipt of your amendments dated:

August 19, 2009	October 23, 2009 [2]	December 17, 2009 [2]
August 22, 2009	November 12, 2009 [2]	January 19, 2010 [2]
September 4, 2009	December 11, 2009 [2]	
October 5, 2009	December 15, 2009	

We also acknowledge receipt of your amendments dated October 23, 2009 [containing Proposed Medguide only REMS] and December 17, 2009 [containing Labeling/ Packaging Information] which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Clinically Important Food Effect

There is a pronounced food effect for your formulation. Food increased mean C_{max} of bupropion by 25% in your food effect study; this increase is equivalent to a dose of about 560 mg. For individual subjects, 67% of subjects (12 out of 18 subjects) in the food effect study showed that food increased C_{max} by >1 fold for your drug compared to the reference. Of these subjects, 2 had an increased C_{max} by >2 fold (2.19 fold and 2.75 fold); a two-fold increase of C_{max} is equivalent to a dose of 900 mg. Four subjects had an increased C_{max} with food to >1.5 fold but < 2 fold; a 1.5-fold increase of C_{max} is equivalent to a dose of 675 mg. Finally, three subjects had an increased C_{max} of > 1.2 fold and < 1.5 fold; a 1.2-fold increase of C_{max} is equivalent to a dose of 540 mg. This finding is of clinical concern because the therapeutic index of the drug, bupropion,

is narrow above the recommended dose (the maximum therapeutic dose is 450 mg/day). The risk of seizure with bupropion increases 10 times with a dose increase from 450 mg to 600 mg.

The risk associated with this food effect is compounded by the fact that patients will necessarily have been titrated from lower doses using the available formulation which can be taken without regard to meals. Therefore, switching a patient from the available formulation to your formulation after using the former for titration has the potential for increasing serious adverse reactions which would not be readily apparent to the prescribing physician or to the patient. At the very least, this problem would require a very intensive educational effort, and you have proposed no such program. It is not clear, however, that any educational effort could effectively address this serious concern. Thus, we have concluded that this serious risk will not be adequately mitigated until your product is reformulated to have a food effect similar to the marketed product.

Product Quality

(1) You have stated that [redacted] (b) (4) will no longer be the drug product manufacturer of your bupropion extended release tablets. Provide the name, address, contact information and CFN # of your new drug product manufacturer. In addition, provide the name, address, contact information and CFN number for all testing (including release, dissolution, and stability) and packaging sites.

(2) Provide complete CMC information to support your new drug product manufacturing site.

(3) The three stability batches (# 07039P-01, 07040P-01, and 07040P-02) were manufactured utilizing [redacted] (b) (4) and do not represent the commercial manufacturing process. Batch (# 08039P-01) was manufactured with [redacted] (b) (4) however, active drug product and placebo tablets were [redacted] (b) (4) and, therefore, is not representative of the commercial process. ICH Q1A (R2) recommends that a minimum of 12 month long-term and 6 month accelerated stability data be submitted at the time of submission. Based on these concerns, we recommend that you submit 12 month of long term and six month of accelerated stability data (with appropriate amount of intermediate stability data, if required) for three batches of drug product representative of the commercial formulation/process manufactured at the new manufacturing site. The previous stability data could be considered as supportive data.

(4) Indicate what acceptance testing is performed (e.g. appearance, identity, purity) by the drug product manufacturer after receiving the drug substance. Provide the analytical procedures used for this testing with validation data if they are different from the USP methods.

(5) Provide a description of the process used in applying the black ink to the tablets.

(6) Your current drug product specification is not representative of your proposed commercial product. Update the current drug product specification to include the proposed tablet printing and logo description. Include the black ink information in the drug product composition table.

(7) Provide individual tablet dissolution data (% dissolved) generated from your stability batches at all stability time points (i.e., 1M, 3M).

(8) Provide open dish stability data of the commercial drug product (including appearance, assay, impurity, and individual tablet dissolution data).

(9) Provide information to demonstrate that the amount of desiccant in your drug product container/closure is optimal. Provide in-use data to show that the product stability is not affected by opening and closing of the container during patient use.

(10) It was noted that six drug product batches had a heat seal problem with the container/closure, which resulted in stability problems. Indicate how this problem has been resolved.

(11) Based on the current manufacturing process, you will need to address the following concerns. If the current formulation or manufacturing process changes, you may need to evaluate the relevance of these concerns with respect to the new manufacturing process/formulation.

(a) In your amendment (dated December 11, 2009), you have stated that the (b) (4) Provide information on how the limit of less than (b) (4) was selected over other (b) (4)

(b) Based on the current batch records, (b) (4) Provide experimental data to justify (b) (4)

(c) In your amendment (dated December 11, 2009), you have stated that (b) (4)

(d) It was noted that three drug product batches had a problem associated with (b) (4) The dissolution profile of the drug product will be compromised if (b) (4) Indicate how this problem has been resolved.

(e) It was noted that two drug product batches had a problem associated with (b) (4) Indicate how this problem has been resolved.

(f) Provide analytical data from batches manufactured at the lower and upper limits of the proposed [redacted] (b) (4) to demonstrate that tablets produced at this [redacted] (b) (4) will meet the product specifications (assay, dissolution and stability).

Labeling

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Other

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	ORIG-1	CARY PHARMACEUTICALS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN
02/03/2010