CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022497Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
Resubmission of NDA 022497

Sponsor:	IntelGenx Corp.
Drug:	Bupropion Hydrochloride 450 mg Extended-Release Tablets
Trade Name:	Forfivo XL
Material Submitted:	Resubmission of 505(b)(2) NDA
Correspondence Date:	May 4, 2011
PDUFA Goal Date:	November 13, 2011

I. Regulatory Background

DPP issued a Complete Response (CR) letter on February 3, 2010 to the originally submitted NDA 022497 by Cary Pharmaceuticals, Inc. mainly due to CMC deficiencies and the clinically significant food effect of Forfivo XL, which potentially could result in significantly increased risk of seizure when Forfivo XL is taken with meal because of the dose-dependent seizure risk with bupropion treatment.

The new sponsor of Forfivo XL, IntelGenx Corp., submitted its response to the CR letter on May 4, 2011. IntelGenx developed a new formulation of Forfivo XL, which has increased coating (b) (4) The sponsor conducted a bioequivalence (BE) study and a food effect study of Forfivo XL. Currently, they seek the approval of this newly-formulated Forfivo XL in the indication of major depressive disorder (MDD) in adult.

II. Materials Reviewed

The following materials were reviewed:

Submission Date	Materials
May 4, 2011	Bioequivalence Study Report Food Effect Study Report Proposed Labeling Case Report Forms Financial Disclosure Certification Debarment Certification

III. Review of Clinical Safety Data

This reviewer examined the clinical safety data of the study (BPO-P0-520), a bioequivalence (BE) and a food effect study with Forfivo XL, and did not find any new safety signals.

This resubmission included the results of Study BPO-P0-520. This was a single-dose crossover, comparative bioavailability study of Bupropion HCl 450 mg XL tablets versus 3 Wellbutrin XL150 mg tablets in healthy non-smoking male volunteers under fasting and fed conditions. The study demonstrated that Forfivo XL 450 mg was bioequivalent to 3 of Wellbutrin XL150 mg tablets and Forfivo XL 450 could be administered without regard to food.

The safety data for this NDA were from healthy male volunteers aged 18 to 47 years. A total of 36 healthy volunteers took two single doses of Forfivo XL 450 mg and one single dose (3 tablets) of Wellbutrin XL 3 x 150mg.

This safety review will focus on serious adverse experiences from the BE and food effect study, which include any deaths, Serious Adverse Events (SAEs) and other adverse events (AEs) that led to dropout from the studies.

A. Deaths

There were no deaths in this study.

B. Non-Fatal SAEs

There were no SAEs in this study.

C. Adverse Events Resulting in Discontinuation

There were no dropouts due to adverse events.

D. Common and Drug-Related Adverse Events

Five (5) (13.9%) of the thirty-six (36) subjects experienced a total of ten (10) mild to moderate AEs. Among these AEs, the treatment emergent possibly drug-related AEs were: upper abdominal pain (1), diarrhea (1) and headache (1).

IV. Quality Review

The CMC review team recommends an approval pending the adequate results of the manufacture site inspection (refer to the review of Pei-I Chu, Ph.D.).

This NDA resubmission did not include the data of *in-vitro* drug alcohol interaction study with the new formulation. However, the ONDQA (Biopharmaceutics) consider this study unnecessary because they expect the newly formulated product with increased coating to have the same or less release of drug in the presence of alcohol compared to the old formulation (refer to the review of Tapash K. Ghosh, Ph.D.).

V. OCP Review

The review team in the Office of Clinical Pharmacology (OCP) recommends an approval of Forfivo XL (refer to the review of Bei Yu, Ph.D.).

The findings of the clinical pharmacology study are summarized in the following:

1. Bioequivalence was demonstrated between Forfivo XL 450 mg and 3 x 150-mg Wellbutrin XL®, the Reference Listed Drug (RLD), with 90% CI of the relative mean C_{max}, AUC $_{(0-t)}$ and AUC $_{(0-\infty)}$ within 80% to 125% in the fasting state.

2. There were no any clinically significant food effects on FORFIVO XL:
   - Food did not affect bupropion Cmax, which is related to the risk of seizure.
   - High-fat food prolonged the drug absorption of bupropion by an average of 7 hours (ranged from 5 - 12 hours) and increased the systemic exposure (AUC) of bupropion by 25%. However, those effects are not considered clinically significant because they are not related to any particular risks such as seizure.

VI. Inspection

Office of Scientific Investigations (OSI) concludes that the clinical and bio-analytical data from the Study (b) (4) are acceptable. The inspection of the drug substance manufacture site is pending.

The Division of Bioequivalence and Good Lab Practice Compliance (DBGC) in OSI conducted inspection of the clinical portion of the study (September 12-16, 2011) and concluded acceptable.

DBGC requested the cancelation of the inspection request for the bio-analytical study conducted at (b) (4) due to the lack of serious observations in their previous experiences in this site including the recent one on (b) (4) and also due to the lack of the resource to complete the inspection before the action goal date. OCP review team concurred with DBGC regarding the cancellation.

The inspection of the drug substance manufacture site is pending, and the CMC review team is following up the inspection result.

VII. Pediatric Plan

The sponsor requested a full waiver in pediatric studies. The Pediatric Review Committee (PeRC) granted the full waiver.

On May 4, 2011, the sponsor requested a full waiver of the PREA (Pediatric Research Equity Act) requirement for pediatric studies. This request is based on the provisions of 21 CFR 314.55(c) (2).

The sponsor asserts that this new ER tablet contains 450 mg of bupropion hydrochloride – the highest approved dose in adults, which would be unsafe in the pediatric age group (0 - 17 years) because bupropion is associated with a dose-dependent and Cmax-related increased risk of seizure.

The Division recommended the full waiver of the pediatric plan to PeRC. PeRC agreed with the Division and granted the full waiver at the PeRC meeting held on September 21, 2011.

VIII. Conclusions and Recommendations

This reviewer recommends an approval action for this resubmission of 505(b) (2) NDA of Forfivo XL if the inspection result of the drug substance manufacture site is acceptable, which is pending at this moment.

Jenn W. Sellers, M.D. Ph.D. FAAP
Medical Reviewer
FDA CDER OND ODE1 DPP
Date: October 21, 2011

cc: HFD-130/JSellers/KAnsah/JZhang/MMathis/TLaughren

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/s/

JENN W SELLERS
10/24/2011

JING ZHANG
10/24/2011

I agree with that the food effect on Forfivo XL is not clinically significant from both safety and efficacy point of view.

Even though high fat food prolonged the drug absorption by an average of 7 hours and increase AUC by 25%, we do not think it will affect the efficacy of Forfive XL because we believes the efficacy of antidepressants is more related to total exposure (AUC) of the drug rather than the Tmax. The PK simulation of steady-state plasma concentration-time profiles based on the single dose study indicated that at steady state the exposure of bupropion following administration of 450-mg FORFIVO XL QD under fed conditions is within the concentration (Cmax and Cmin) window of bupropion after administration of Wellbutrin
XL at 3 x 150 mg daily dosing under fasted conditions.

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 1, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for complete response action for Bupropion HCl 450 mg ER tablets for MDD

TO: File NDA 22-497
[Note: This overview should be filed with the sponsor's 3-31-09 original submission.]

Background

This is a 505(b)(2) application for an extended release (once daily) formulation of bupropion hydrochloride. The sponsor has produced only one tablet strength, i.e., 450 mg. The RLD for this product is Wellbutrin XL (150 mg and 300 mg). The rationale for this 450 mg product is to provide for a more convenient formulation for patients who need this highest recommended dose. The basis for this application is CMC information intended to support this new formulation and bioequivalence data that the sponsor feels adequately demonstrate bioequivalence for these two formulations. The sponsor was also required to conduct a food effect study and an *in vitro* alcohol interaction study. Although Wellbutrin XL is approved for both MDD and seasonal affective disorder, the sponsor for this new formulation is seeking a claim only for MDD. The work in support of this application was done under IND (b) (4) We held a pre-IND meeting with the sponsor on 1-30-07 and an EOP2 meeting on 1-14-08.

Summary of Conclusions and Recommendations from Review Teams

CMC

The CMC reviewer was Pei-I Chu, Ph.D. There are numerous serious CMC deficiencies with this application, including the fact that there is no identified drug product manufacturer. The original manufacturer, (b) (4) was taken over by (b) (4) and this new company has indicated that it has no agreements to manufacture this product. In addition, there are other serious problems with the stated manufacturing process and other CMC issues, and these problems will be detailed in the CR letter. The CMC group has recommended a CR action for this application, and I agree.

Pharm/Tox

There are no pharm/tox deficiencies at this time.

OCP

The OCP review was conducted by Bei Yu, Ph.D. The sponsor conducted two *in vivo* studies, i.e., a single-dose bioequivalence (BE) study under fasted conditions, and a food effect study. They also conducted an *in vitro* alcohol interaction study to observe for possible dose dumping.

BE Study: The BE study, comparing their new product (bupropion 450 mg) to Wellbutrin XL 150 mg (3 tablets), demonstrated bioequivalence for the parent (bupropion) and two of the active metabolites (hydroxybupropion and erythrohydrobupropion), but just missed for the third active metabolite (threohydrobupropion). This metabolite was slightly more available from the new formulation (point estimate 1.13; 90% CI [96-132%]). Given that this metabolite contributes only 15% of the overall activity, a 13% increase would contribute only another 2% to the overall activity. This difference is of no clinical consequence.

Food Effect Study: The food effect study, however, revealed a serious problem. Food increases the absorption time by 2.5 hours (from 5 to 7.5 hours) and, importantly, increases the Cmax to a clinically significant extent. Out of 18 subjects in the study:

-2 had an increase greater than 2-fold (1 was 2.19-fold and the other, 2.75-fold). A 2-fold increase is equivalent to a dose of about 900 mg.

-4 had an increase between 1.5 and 2-fold. A 1.5-fold increase is equivalent to a dose of about 675 mg.

-3 had an increase between 1.2 and 1.5-fold. A 1.2-fold increase is equivalent to a dose of about 540 mg.

Increases in Cmax in this range are important because the risk of seizure with bupropion increases about 10-fold with dose increases from 450 mg to 600 mg. The importance of this food effect is exacerbated by the fact that patients need to be titrated to the 450 mg/day dose. Thus, patients would need to be titrated up with Wellbutrin XL, which can be given without regard to food (no food effect). Once stabilized on Wellbutrin 450 mg/day they would be switched to this new formulation. Such a switch could place a large fraction of patients at a greatly increased risk of having seizures. One approach would be a very extensive educational program to ensure that prescribers and patients understood that this new formulation cannot be taken with food, and no such program has been proposed. Even with such a program, however, it seems likely that many patients would consume this new formulation with food and have a substantial risk of seizures. Since there is no advantage to this new formulation, other than the minor advantage of having to take only 1 table rather than 2 or 3, this formulation can hardly be justified.

Alcohol Interaction Study: This in vitro study did reveal a potentially clinically relevant dose dumping effect (22% dissolution at 2 hours) only at the highest concentration (40% EtOH concentration). In my view, this is not a realistic circumstance (i.e., having a 40% EtOH concentration in the stomach).

The OCP group has recommended a CR action based primarily on the significant food effect, and I agree.

Clinical

This application was reviewed by Jenn Sellers, M.D., from the clinical group. There were no important adverse events reported in the two clinical studies in this program. The main clinical concern is the same concern expressed by the OCP group, i.e., a very significant food effect.

DMEPA:

DMEPA has approved the proposed name for this product, i.e., "Forfivo".

As have other groups, DMEPA has expressed a concern that the food effect could lead to serious adverse events without an exceptionally effective educational program. No such program has been proposed.

DSI

The site at which the MD bioequivalence study was conducted was inspected, and the DSI memo raises a concern that regulatory requirements were not strictly followed, in that samples were not retained at the study site. This issue was also noted in the medical officer review. I have discussed this issue with OCP staff, and they confirmed for me that they have complete confidence in the data and the finding of bioequivalence. Regarding sample retention, they noted that the samples were simply sent off for storage at another site, and would be readily available if needed. Thus, I do not consider this a particularly important issue for this application.

Labeling

Given all the problems with this application, we have not drafted labeling to send with the CR letter.

Conclusions and Recommendations

I will issue a CR letter, noting that the critical CMC deficiencies and the OCP deficiency.

cc:
Orig NDA 22-497
HFD-130/TLaughren/MMathis/JZhang/JSellers/KAnsah

DOC: Bupropion HCl 450 ER_NDA22497_Laughren_CR Memo.doc

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

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/s/

THOMAS P LAUGHREN
02/01/2010

Review and Evaluation of Clinical Data
NDA 022497

Sponsor:	Cary Pharmaceuticals, Inc.
Drug:	Bupropion Hydrochloride 450 mg Extended-Release Tablets
Trade Name:	Forfivo
Material Submitted:	505(b)(2) New Drug Application
Correspondence Date:	March 31, 2009
PDUFA Goal Date:	February 6, 2010

I. Regulatory Background

Cary Pharmaceuticals, Inc. of Great Falls, Virginia has developed an extended-release tablet containing 450 mg bupropion hydrochloride (BUP-450) under IND (b) (4) During the drug development, Pre-IND meeting was held on January 30, 2007 and the EOP2 meeting was held on July 14, 2008. At the Pre-IND meeting, the Division required Cary Pharmaceuticals to do a food-effect study in addition to what they proposed bioequivalence study. At the EOP2 meeting, the Division advised Cary Pharmaceuticals to do an alcohol dose dumping study to look at the *in vitro* effect of alcohol on dosing.

On March 31, 2009, Cary Pharmaceuticals submitted NDA 22-497 under the provision of section 505(b) (2) of the Federal Food Drug, and Cosmetic Act to obtain marketing approval of BUP-450mg XL once daily for the indication of major depressive disorder (MDD). The reference listed drug (RLD) product is Wellbutrin XL (bupropion hydrochloride) 150 mg Extended-Release Tablets, GlaxoSmithKine (GSK) approved on 08/28/2003 under NDA 021515. Wellbutrin XL is indicated in the treatment of MDD and seasonal affective disorder in the dosage forms of 150 mg and 300 mg. Cary Pharmaceuticals plans only to seek the indication of MDD and not the seasonal affective disorder. Bupropion hydrochloride 450 mg/day given as a single dose is an approved dose in the treatment of MDD in adult, but not an approved strength of Wellbutrin XL® (requiring administration of 150 and/or 300 mg tablets). BUP-450 is a new higher strength formulation of the currently marketed bupropion hydrochloride drug product for which the highest strength is 300 mg.

Early December 2009, FDA inspector Bruce McCullough was informed that in July, 2009, (b) (4) bought (b) (4) which was the manufacture site for BUP-450. (b) (4) informed Bruce that they have no agreements or contracts with Cary to manufacture BUP 450 XL and they do not intend to pursue it. Therefore, currently Cary does not have a manufacture site for BUP 450 XL.

DPP and Cary held a teleconference on 12/16/09 regarding the drug product manufacture site. DPP also informally discussed with Cary regarding a number of other issues such as the food effect of the product, the increased risk of seizure due to the increased Cmax by food and some CMC issues.

II. Materials Reviewed

The following materials were reviewed.

Submission Date	Materials
March 31, 2009	Bioequivalence Study Report (3631) Food Effect Study Report (S08-0027) JMP Datasets Proposed Labeling PREA Waiver Request Case Report Forms Financial Disclosure Certification Waiver Request for PREA Debarment Certification Patent Certification FDA PIND and EOP2 Meeting Minutes

III. Financial Disclosure

On 03-31-06, Douglas D. Cary, President and CEO of Cary Pharmaceuticals, Inc. certified that Cary had not entered into any financial arrangement with the principal or sub-investigators from studies 3631 and S08-0027 whereby the value of the compensation could have been affected by the outcome of the study. Also, he certified that each investigator required to disclose a proprietary interest in the product or significant equity interest in the sponsor did not disclose any such interests. He further certified that none of these investigators was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

IV. Review of Clinical Safety Data

During the development, BUP-450 XL was evaluated in the following 3 studies:

1. A BUP 450 XL Bioequivalence Study (Protocol No. 3631): A two-way crossover, open-label, single-dose, fasting, bioequivalence study of Bupropion HCI 450 mg XL tablets versus Wellbutrin XL150 mg tablets in normal, healthy, non smoking male and female subjects.

2. A BUP 450 XL Effect of Food Study (Protocol No. S08-0027): A food effect study of 450 mg bupropion HCL extended-release tablet (BUP-450) and 3 x 150 mg Wellbutrin XL extended-release tablets in two cohorts.

3. In vitro alcohol dumping effect study

The safety data for this NDA were derived from the bioequivalence study (Protocol 3631) and the food effect study (Protocol S08-0027) in healthy male and female volunteers aged 18 to 56 years. A total of 35 subjects received 1 dose (1 tablet) of BUP 450 XL in the bioequivalence study. A total of 18 subjects received 2 doses (1 in fed and 1 in fasted condition; one dose = 1 tablet) and 2 subjects only received 1 dose of BUP 450 XL (1

subject was in the fed condition and the other was in the fasted condition) in the effect of food study.

This safety review will focus on serious adverse experiences from the bioequivalence study and the food effect study, that is, any deaths, Serious Adverse Events (SAEs) and other adverse events (AEs) that led to dropout from the studies.

A. Deaths

There were no deaths in both studies.

B. Non-Fatal SAEs

There were no SAEs in both studies.

C. Adverse Events Resulting in Discontinuation

In the bioequivalence study (Protocol 3631), 4 of 39 discontinued due to adverse events:

- Subject 029 – headache and sneezing.
- Subject 033 – rash and itchiness over rash.
- Subject 039 – rash and itchiness over rash.
- Subject 034 – upper respiratory infection

In the food effect study (Protocol S08-0027), 1 of 20 discontinued due to an adverse event:

- Subject 06 – vomiting.

None of these adverse events is considered unexpected with BUP 450 XL.

D. Common and Drug-Related Adverse Events

AEs were mainly in the Nervous System Disorders, Gastrointestinal Disorders, and Skin and Subcutaneous Disorders systems. Most AEs were mild in intensity. All the AEs can also be found in the Wellbutrn XL Package Insert.

V. OCP Review

Bioequivalence (BE), the food effect data and the alcohol dumping effect in vitro study are reviewed in detail by the OCP review team. The following is the summary.

1. Bioequivalence was demonstrated between BUP 450 XL and the RLD Wellbutrin XL 150mg.

2. There was a food effect on BUP 450 XL. Food significantly increased Cmax for BUP 450 XL and thus significantly increased the risk of Cmax related seizure. It increased mean Cmax by 25%. 67% subjects (12/18) have increased Cmax 1.01 -

2.75 folds on the fed condition which is equivalent to a dose of BUP 450 XL 454mg to 1238mg. Food has increased a dose to more than 675mg in 22% (4/18) of subjects and more than 900mg in 11% (2/18) of subjects.

3. There was an alcohol dumping effect. The presence of 40% of alcohol caused a 22% increase in dissolved bupropion HCl.

OCP recommended not approve BUP 450 XL.

VI. DSI Inspection

The Division of Scientific Investigations (DSI) was consulted by DPP on May 28, 2009 for inspection of study 3631 for both its clinical and analytical aspects. According to the memorandum dated November 10, 2009 by DSI, inspection found that (b) (4) did not retain the test and reference products at the clinical study site which is required by the regulations. Therefore, the authenticity of the products used in Study 3631 cannot be confirmed.

FDA inspector Bruce McCullough was not able to do the inspection scheduled in December 2009 due to the fact that Cary has lost the manufacture site for BUP 450 XL.

VII. Assessment from the Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA showed significant concerns regarding the approval of this product from a drug safety and medication error perspective. They are concerned with the increased risk of seizure if Forfivo is taken with food. There are several other currently marketed Bupropion products (Wellbutrin XL, Wellbutrin SR, Wellbutrin IR, Zyban, Aplenzin, and generic Bupropion products) that do not have a food effect and may be taken with or without food. Bupropion was initially approved in 1985. Healthcare professionals have more than 20 years of experience with Buproprion, and are used to prescribing and/or dispensing Buproprion without providing specific instructions to patients regarding food intake. DMEPA does not believe that the product labeling with respect to a food effect would be adequate to ensure the communication of this important information to healthcare providers and patients. DMEPA believe that confusion and medication errors might occur due to the food effect of Forfivo.

VIII. Pediatric Plan

On 03-31-2009, Cary Pharmaceuticals requested a full waiver of the PREA (Pediatric Research Equity Act) requirement for pediatric studies. This request is based on the provisions of 21 CFR 314.55(c) (2) for a new extended-release tablet containing 450 mg of bupropion hydrochloride.

The reason for waiver is that the product (BUP-450 XL) would be unsafe in the pediatric age group (0 - 18 years) because of the increased risk of seizures associated with high doses of bupropion at Cmax. The risk of seizures has been shown to be dose-dependent. The usual target dose in adults is 300 mg/day, given once daily in the morning. For those patients who do not respond to 300 mg/day, the dose can be further

increased to a maximal dose of 450 mg/day, the highest approved dose of bupropion hydrochloride in adults.

Cary Pharmaceuticals argues that strong evidence suggests that this product would be unsafe in all pediatric age groups. He believes that the above reason is justification to grant a waiver of pediatric assessment requirements.

This consideration appears to meet the PREA provisions for granting a full waiver. I recommend that a full waiver be granted.

IX Conclusions and Recommendations

Bupropion has dose-related risk for seizures. Seizure incidence increases 10-fold between a dose 450 mg/day and 600 mg/day. The risk of seizure is increased even more significantly at a dose > 600mg. According to A 3-year multi poison center cohort study of hospitalized patients with ingestion of bupropion XL ≥600 mg in adults and ≥4 mg/kg in children, 31.6% (31/117) of patients developed seizures (Starr, P. et al. 2009). Since Forfivo XL has a significant food and alcohol effect, the risk of seizures is significantly increased if it is taken with food and/or alcohol.

I concur with the recommendations from OCP and DMEPA. I recommend not approve BUP-450 XL, Forfivo.

Jenn W. Sellers, M.D. Ph.D. FAAP
Medical Reviewer
FDA CDER OND ODE1 DPP

Date January 29, 2010

Reference:
Starr, P et al. Incidence and Onset of Delayed Seizures after Overdoses of Extended-Release Bupropion. Journal of Emergency Medicine (2009) 27, 911–915.

cc: HFD-130/
JSellers
KAnsah
JZhang
MMathis
TLaughren

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

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JENN W SELLERS
01/29/2010

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