

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022497Orig1s000**

**OTHER REVIEW(S)**

## SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22497
APPLICANT	Intelgenx Corporation
PRODUCT NAME	Forfivo XL (bupropion hydrochloride)
SUBMISSION DATE	May 13, 2011
PDUFA DATE	November 13, 2011
SEALD SIGN-OFF DATE	November 9, 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed November 8, 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/  
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LAURIE B BURKE  
11/09/2011

## SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22497
APPLICANT	Intelgenx Corporation
PRODUCT NAME	Forfivo XL (bupropion hydrochloride)
SUBMISSION DATE	May 13, 2011
PDUFA DATE	November 13, 2011
SEALD REVIEW DATE	November 8, 2011
SEALD LABELING REVIEWER	Debra Beitzell, BSN

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. **Waiver of ½ page HL limit to be granted by DPP.**
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval. **Please insert revision month and year upon approval.**

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

### • General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

### • Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions). **Warning for “Psychiatric Events and Smoking Cessation” to be discussed with DAAP and DPP as a class labeling revision.**

### • Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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DEBRA C BEITZELL  
11/08/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**PATIENT LABELING REVIEW**

Date: **October 26, 2011**

To: **Thomas Laughren, MD, Director  
Division of Psychiatry Products (DPP)**

Through: **LaShawn Griffiths, RN, MSHS-PH, BSN  
Patient Labeling Reviewer, Acting Team Leader,  
Division of Risk Management (DRISK)**

**Melissa Hulett, MSBA, BSN, RN  
Patient Labeling Reviewer, Acting Team Leader  
Division of Risk Management**

From: **Sharon W. Williams, MSN, BSN, RN  
Patient Labeling Reviewer  
Division of Risk Management**

Subject: **DRISK Review of Patient Labeling (Medication Guide)**

Drug Name (established name): **FORFIVO XL (bupropion hydrochloride)**

Dosage Form and Route: **Extended-Release Tablets**

Application Type/Number: **NDA 22-497**

Applicant: **Cary Pharmaceuticals, Inc**

OSE RCM #: **2011-1819**

## 1 INTRODUCTION

Cary Pharmaceuticals Inc. submitted a New Drug Application (NDA) for FORFIVO XL Extended Release Tablets on March 31, 2009 for the proposed indication of major depressive disorder in adults. On February 3, 2010 the agency issued a Complete Response (CR) letter to Cary Pharmaceuticals related to the issues of clinically important food effects and product quality.

On May 4, 2011, IntelGenx Corp. submitted its response to the CR letter as the Applicant (sponsor) of record for FORFIVO XL.

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to provide a review of the Applicant's proposed Medication Guide (MG) for FORFIVO Extended Release Tablets.

## 2 MATERIAL REVIEWED

- Draft FORFIVO XL Extended Release Tablets Medication Guide (MG) received on May 4, 2011 and revised by the review division throughout the review cycle and sent to DRISK on October 20, 2011.
- Draft FORFIVO XL Extended Release Tablets Prescribing Information (PI) received May 4, 2011 revised by the Review Division throughout the current review cycle and received by DRISK on October 20, 2011.
- Approved WELLBUTRIN XL (bupropion hydrochloride) comparator labeling revised July 26, 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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immediately following this page.

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SHARON W WILLIAMS  
10/26/2011

LASHAWN M GRIFFITHS  
10/26/2011

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** October 14, 2011

**To:** Kofi Ansah, PharmD  
Regulatory Project Manager  
Division of Psychiatry Products (DPP)

**From:** Jessica Cleck Derenick, PhD  
Regulatory Review Officer  
Division of Professional Promotion  
Office of Prescription Drug Promotion (OPDP)

Susannah K. Hubert, MPH  
Regulatory Review Office  
Division of Direct-to-Consumer Promotion  
OPDP

**Subject: OPDP Comments on FORFIVO XL (bupropion hydrochloride) extended-release tablets, NDA 022497**

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OPDP has reviewed the proposed product labeling (PI) for FORFIVO XL (bupropion hydrochloride) extended-release tablets (FORFIVO) as requested in the consult dated June 16, 2011.

The following comments, using the proposed PI posted in the E-room on October 14, 2011, by Kofi Ansah, are provided directly on the attached, marked-up version of the label.

Please feel free to contact us with any questions or clarifications.

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/s/

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JESSICA N CLECK DERENICK  
10/14/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 13, 2011

To: Jenn Sellers, M.D.  
Medical Officer  
Division of Psychiatry Products  
Office of Drug Evaluation I

Through: Judy Staffa, Ph.D., R.Ph.  
Director  
Division of Epidemiology II  
Office of Surveillance and Epidemiology

Grace Chai, Pharm.D.  
Acting Drug Use Data Analyst Team Leader  
Division of Epidemiology II  
Office of Surveillance and Epidemiology

From: Kusum Mistry, Pharm.D.  
Drug Use Data Analyst  
Division of Epidemiology II  
Office of Surveillance and Epidemiology

Subject: Bupropion 450 mg Drug Utilization

Drug Name(s): Bupropion hydrochloride and bupropion hydrobromide

Application Type/Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: 2011-2570

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

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## EXECUTIVE SUMMARY

The Division of Epidemiology II (DEPI II) was tasked by the Division of Psychiatry Products (DPP) to provide drug utilization data for bupropion. The main purpose of this review is to evaluate a sponsor's resubmission of a new drug application for a new formulation of bupropion hydrochloride 450 mg extended-release (XR). This review provides U.S. outpatient retail pharmacy utilization trends for bupropion hydrochloride from July 2006 through June 2011 and bupropion hydrobromide from July 2008 through June 2011.

### *Summary of findings for Bupropion HydroChloride from July 2006 through June 2011:*

- Approximately (b) (4) patients received a dispensed prescription for bupropion hydrochloride from U.S. outpatient retail pharmacies.
- A daily dose of 450 mg accounted for about (b) (4) of use when bupropion hydrochloride use by daily dose was reported by office-based physicians' practices.
- The top strength associated with the use of a daily dose of 450 mg of bupropion hydrochloride 450 mg was the "150 mg strength".
- The most common directions of use (signa) associated with the use of bupropion hydrochloride 150 mg strength was "3 per day".

### *Summary of findings for Bupropion HydroBromide (Aplenzin™) from July 2008 through June 2011:*

- Approximately (b) (4) patients received a dispensed prescription for Aplenzin™ from U.S. outpatient retail pharmacies.
- Approximately (b) (4) of drug occurrences in office-based physician practices were associated with the use of Aplenzin™ 522 mg, the only strength of Aplenzin™ equivalent to bupropion hydrochloride 450 mg per day.
- The only directions of use (signa) associated with the use of Aplenzin™ 522 mg strength was "once a day."

## 1 BACKGROUND

### 1.1 INTRODUCTION

The Division of Psychiatry Products (DPP) is evaluating the extent of bupropion hydrochloride use for a daily dose of 450 mg to help determine the need for a new 450 mg extended release dosage formulation and strength. This request was prompted by a resubmission of a new drug application by the sponsor, Intelgenx, to propose a new formulation of bupropion hydrochloride 450 mg XR (Forfivo XL®). In support of this review, the Division of Epidemiology II (DEPI II) has been requested to provide drug

utilization data for bupropion. Specifically, we were asked to analyze the total number of patients, total daily dose, and directions for use (signa) associated with the use of bupropion 450 mg. To provide a comprehensive analysis at the molecule level, bupropion *hydrochloride* and bupropion *hydrobromide* products were both examined. Using the currently available proprietary drug use databases licensed by the Agency, this review provides outpatient retail drug utilization data for bupropion hydrochloride in the U.S. population from July 2006 through June 2011 and for bupropion hydrobromide from July 2008 through June 2011.

## 1.2 PRODUCT INFORMATION

Bupropion hydrochloride is an atypical antidepressant and smoking cessation aid of the aminoketone class and is chemically unrelated to tricyclic, selective serotonin reuptake inhibitor (SSRI), or other known antidepressants agents.<sup>1</sup> Bupropion inhibits the neuronal reuptake of norepinephrine and dopamine. Bupropion hydrochloride is currently available in three formulations: immediate-release, sustained-release (SR), and extended-release (XL) (Table 1).

Bupropion was recently marketed as a hydrobromide salt under the trade name Aplenzin™ by Sanofi-Aventis. Aplenzin™ is specifically indicated for the treatment of major depressive disorder.<sup>2</sup> Aplenzin™ differs from other generic and branded bupropion hydrochloride antidepressants because it provides a hydrobromide salt extended-release formulation, offering prescribers the benefit with one tablet of once-daily dosing at all doses. In addition, Aplenzin™ 522 mg strength is the only FDA-approved single-tablet that is a once daily treatment that is equivalent to 450 mg of bupropion hydrochloride therapy, which requires two or three tablets daily.

**Table 1: Bupropion Formulations<sup>3</sup>**

Generic and Trade Name	Application Number	Original Approval Date	Dosage Form(s) and Strength	Manufacturer
<b>Bupropion HydroChloride</b>				
Wellbutrin®	NDA 18-644	12/30/1985	Tablet, immediate-release: 75 mg, 100 mg	GlaxoSmithKline
Wellbutrin SR®	NDA 20-358	10/04/1996	Tablet, sustained-release: 100 mg, 150 mg, 200 mg	GlaxoSmithKline
Wellbutrin XL®	NDA 21-515	08/29/2003	Tablet, extended-release: 150 mg, 300 mg	GlaxoSmithKline

<sup>1</sup> Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, and Zyban® package inserts. GlaxoSmithKline. Research Triangle Park, NC (2010).

<sup>2</sup> Aplenzin™ package insert. Sanofi-Aventis, Bridgewater, NJ; (2009).

<sup>3</sup> Bupropion, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations Web site. <http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm>. Accessed August 01, 2011.

**Table 1 Continued: Bupropion Formulations<sup>4</sup>**

Generic and Trade Name	Application Number	Original Approval Date	Dosage Form(s) and Strength	Manufacturer
<b>Bupropion HydroChloride</b>				
Zyban <sup>®</sup>  Generic bupropion HCl	NDA 20-711  Multiple Abbreviated	05/14/1997  Multiple	Tablet, extended-release: 150 mg  Tablet: 75 mg, 100 mg  Tablet, extended-release: 100 mg, 150 mg, 200 mg, 300 mg	GlaxoSmithKline  Multiple
<b>Bupropion HydroBromide</b>				
Aplenzin <sup>™</sup>	NDA 22-108	04/23/2008	Tablet, extended release: 174 mg, 348 mg, 522 mg  174 mg bupropion HBr equivalent to 150 mg bupropion HCl  348 mg bupropion HBr equivalent to 300 mg bupropion HCl  <b>522 mg bupropion HBr is equivalent to 450 mg bupropion HCl</b>	Sanofi-Aventis U.S.A

## 2 METHODS AND MATERIALS

### 2.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives<sup>™</sup> Sales Perspectives (see *Appendix 3* for full database description) was used to determine the various retail and non-retail channels of distribution for bupropion hydrochloride. Sales data for 12-month period ending May 2011 indicated that approximately (b)(4) of bupropion packages and bottles (Eaches) were distributed to outpatient retail pharmacies; (b)(4) to non-retail; and (b)(4) to mail order pharmacies<sup>5</sup>. As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

<sup>4</sup> Bupropion, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations Web site. <http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm>. Accessed August 01, 2011.

<sup>5</sup> IMS Health, IMS National Sales Perspectives<sup>™</sup> Database. MAT 2010. Extracted August 2011. File: 1108bupr.xls.

## 2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see *Appendix 3*).

SDI, Vector One<sup>®</sup>:Total Patient Tracker (TPT) was used to obtain estimates of the projected number of patients who received a prescription for bupropion hydrochloride from U.S. outpatient retail pharmacies from July 2006 through June 2011 and bupropion hydrobromide from July 2008 through June 2011. SDI, Physician Drug & Diagnosis Audit (PDDA) was used to obtain total daily doses and directions for use (signa) associated with the use of bupropion hydrochloride 450 mg according to U.S. office-based physician practices from July 2006 through June 2011 and bupropion hydrobromide from July 2008 through June 2011.

## 2.3 PRODUCTS INCLUDED

Bupropion hydrochloride products: Wellbutrin<sup>®</sup>, Wellbutrin SR<sup>®</sup>, Wellbutrin XL<sup>®</sup>, Zyban<sup>®</sup>, and generic bupropion hydrochloride products

Bupropion hydrobromide product: Aplenzin<sup>™</sup>

## 3 RESULTS

### 3.1 BUPROPION HYDROCHLORIDE ANALYSIS

#### 3.1.1 Patient Data for Bupropion HydroChloride

*Figure 1* in *Appendix 1* graphically displays the projected number of patients who received a dispensed prescription for bupropion hydrochloride from U.S. outpatient retail pharmacies from July 2006 through June 2011. Approximately (b) (4) patients received a prescription for bupropion hydrochloride during the aggregate time period. The total number of patients who received a bupropion hydrochloride prescription decreased by (b) (4) from about (b) (4) patients in the 12-month period ending June 2007 to approximately (b) (4) patients in the 12-month period ending June 2011.

#### 3.1.2 Total Daily Dosage of 450 mg Associated With the Use of Bupropion HydroChloride

*Table 2* in *Appendix 1* provides the projected number of drug occurrences<sup>6</sup> of bupropion hydrochloride, stratified by total daily dosage of 450 mg, as reported by office-based physician practices from July 2006 through June 2011. Approximately (b) (4) of bupropion hydrochloride drug occurrences by total daily dose were of 450 mg per day, (b) (4) of drug occurrences were of less than 450 mg per day and less than (b) (4) of drug occurrences were of greater than 450 mg per day during the aggregate time period. The number of

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<sup>6</sup> “Drug occurrences” refers to the number of times a product has been reported on a patient information form during an office-based patient visit for that time period. Please see further explanation in the “Limitations” section.

bupropion hydrochloride drug occurrences for 450 mg per day appears to decrease from the 12-month period ending June 2007 to the 12-month period ending June 2011

### **3.1.3 Directions for Use by Strength Associated With the Use of Bupropion Hydrochloride 450 mg per Day**

*Table 3* in *Appendix 1* provides the projected number of drug occurrences for the most common physician intended directions for use (signa), stratified by strength, for a daily dose of bupropion hydrochloride 450 mg, as reported by office-based physician practices from July 2006 through June 2011. The most common strength associated with the use of bupropion hydrochloride 450 mg per day was the 150 mg strength with (b) (4) of drug occurrences, followed by the 75 mg strength with (b) (4) of drug occurrences. The most common dosing regimen for patients associated with the use of the bupropion hydrochloride 150 mg strength were “3 tablets per day”, accounting for (b) (4) of drug occurrences. The most common dosing regimen for patients associated with the use of the bupropion hydrochloride 75 mg strength were “2 tablets three times a day”, accounting for (b) (4) of drug occurrences.

## **3.2 BUPROPION HYDROBROMIDE (APLENZIN™) ANALYSIS**

### **3.2.1 Patient Data for Bupropion Hydrobromide**

*Figure 2* in *Appendix 1* graphically displays the projected number of patients who received a dispensed prescription for Aplenzin™ from U.S. outpatient retail pharmacies from July 2008 through June 2011. Approximately (b) (4) patients received a prescription for Aplenzin™ during the aggregate time period. Since its approval in year 2008, the total number of patients who received an Aplenzin™ prescription increased by (b) (4) from nearly (b) (4) patients in the 12-month period ending June 2009 to (b) (4) patients in the 12-month period ending June 2011. *Table 4* in *Appendix 1* provides the projected number of patients who received a dispensed prescription for bupropion hydrobromide (Aplenzin™) stratified by strength, from U.S. outpatient retail pharmacies from July 2008 through June 2011. Patients who received a prescription for Aplenzin™ 522 mg (equivalent to 450 mg of bupropion hydrochloride) accounted for (b) (4) patients (b) (4) during the examined time period. Patients who received a prescription for Aplenzin™ 522 mg increased by (b) (4) from (b) (4) patients in the 12-month period June 2009 to (b) (4) patients in the 12-month period ending June 2011.

### **3.2.2 Total Daily Dosage Associated With the Use of Bupropion Hydrobromide**

*Table 5* in *Appendix 1* provides the projected number of drug occurrences for bupropion hydrobromide (Aplenzin™), stratified by total daily dosage, as reported by office-based physician practices from July 2008 through June 2011. Approximately (b) (4) of Aplenzin™ drug occurrences were equivalent of 450 mg per day of bupropion hydrochloride and (b) (4) of drug occurrences were equivalent of less than 450 mg per day of bupropion hydrochloride during the cumulative time period. Since its approval in year 2008, the number of drug occurrences for Aplenzin™ 522 mg per day (equivalent to 450 mg per day of bupropion hydrochloride) appears to increase from the 12-month period

ending June 2009 to the 12-month period ending June 2011. The directions for use (signa) for all bupropion hydrobromide (Aplenzin™) products as reported by office-based physician practices, were for “once a day” (data not shown).

#### 4 DISCUSSION

Based on the databases used for this analysis, the data shows that there appears to be drug utilization for bupropion 450 mg daily. During the 12-month period ending June 2011, (b) (4) patients received a prescription for bupropion hydrochloride and (b) (4) patients received a prescription for Aplenzin™. Approximately (b) (4) of patients dispensed Aplenzin™ received the 522 mg strength (equivalent to 450 mg of bupropion hydrochloride) during the examined time period. Analysis of bupropion hydrochloride by total daily dose showed over (b) (4) of use was for daily doses of 450 mg or higher. These findings suggest that clinicians are prescribing bupropion hydrochloride 450 mg per day and higher.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that (b) (4) of bupropion products were distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives™. This review does not include community mental health centers, outpatient clinics, and various other clinical settings where patients receive mental health care. It is unknown what percentage of overall bupropion 450 mg per day treatment is utilized in different settings; therefore, our results should be viewed with caution. Sales data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

We focused our analysis on only the outpatient retail pharmacy; therefore these estimates may not apply to other settings of care in which these products are used (e.g. mail order). The estimates provided are national estimates from retail pharmacy dispensing, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Total daily dose and directions for use (signa) were obtained using SDI’s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time. SDI recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

SDI uses the term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a

prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these. SDI recommends caution interpreting projected annual “drug occurrences” or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals; therefore data is very weak and can not be used for trend analysis.

## 5 CONCLUSIONS

In the U.S. outpatient retail pharmacy setting, approximately (b) (4) million patients received a prescription for bupropion hydrochloride from July 2006 through June 2011 and (b) (4) patients received a prescription for Aplenzin™ from July 2008 through June 2011. According to U.S. office-based physician practices, approximately (b) (4) of drug occurrences were associated with bupropion hydrochloride 450 mg per day and (b) (4) of drug occurrences were associated with Aplenzin™ 522 mg (equivalent to bupropion hydrochloride). The most common strength associated with the use of bupropion hydrochloride 450 mg per day was the 150 mg strength, written as “3 tablets per day” as reported by office-based physician practices.

The findings from this analysis suggest that a daily dose of bupropion hydrochloride 450 mg per day was observed during the examined time period and the data will assist the Division of Psychiatry Products to evaluate bupropion 450 mg utilization.

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## **APPENDIX 3: DATABASE DESCRIPTIONS**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **SDI's Vector One®: Total Patient Tracker (TPT)**

The SDI, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

### **SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel**

The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/  
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KUSUM S MISTRY  
10/12/2011  
Cleared by Data Vendors

GRACE P CHAI  
10/12/2011

JUDY A STAFFA  
10/14/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: October 12, 2011

Reviewer(s): Richard A Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Lubna Merchant, MS, PharmD, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength: Forfivo XL (Bupropion HCl Extended-release Tablets)  
450 mg

Application Type/Number: NDA 022497

Applicant/sponsor: IntelGenx Corp

OSE RCM #: 2011-1817

## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the proposed container label and insert labeling for Forfivo XL (Bupropion HCL Extended-release Tablets) for NDA 022497 for areas of vulnerability to confusion that could lead to medication errors.

### 1.1 REGULATORY HISTORY

Forfivo XL (Bupropion HCl Extended-release Tablets) NDA 022497, is a 505(b)(2) application. The reference listed drug is Wellbutrin XL 150 mg tablets. The Division of Psychiatry Products (DPP) issued a Complete Response on February 3, 2010 secondary to safety issues around the fact the product had significant changes to the pharmacokinetic profile when taken with food. Subsequently, the application was sold to IntelGenX Corp who revised the formulation and resubmitted the application May 13, 2011.

### 1.2 PRODUCT INFORMATION

Forfivo XL (Bupropion Extended-release Tablets) is indicated for major depressive disorder for patients requiring the maximum daily dose (450 mg) of Bupropion HCl. The dose is one tablet (450 mg) by mouth once daily. The extended-release tablets are available in the 450 mg strength only and are packaged in bottles with a (b) (4) closure containing 30 tablets. The white oval tablets include "Forfivo" printed on one side and no score line on either side. The bottles are stored at room temperature.

In comparison, the reference listed drug, Wellbutrin XL, is a round white tablet with the product name and strength (either, 150 mg or 300 mg) on one side.

## 2 METHODS

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 8, 2011 (Appendix A)
- Insert Labeling submitted September 8, 2011

### 2.1 SELECTION OF WELLBUTRIN XL MEDICATION ERROR CASES

Since the reference listed drug, Wellbutrin XL, is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Wellbutrin XL. The September 2, 2011 AERS search used the following search terms: active ingredient "Bupropion Hydrochloride", trade name "Wellbutrin XL", and verbatim terms "Bupropion%," limiting term selection to those containing "Daily," "ER," "Extended release," "once a day," "XL," or "XR" and "Wellbutrin XL%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors"

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

and “Product Quality Issues”. The time frame was limited to January 1, 2011 forward to identify the most recent cases. Although the time frame was limited to less than one year, the search yielded a total of 168 reports. Appendix B lists the ISR numbers of the reports retrieved.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error, describe errors involving bupropion immediate release or the twice daily sustained-release formulations, cases in which Wellbutrin XL or generic equivalent was identified as a concomitant medication and not involved in the medication error, describe product complaint, describe an accidental pediatric ingestion, or describe an intentional drug overdose.

### **3 RESULTS AND DISCUSSION**

The following sections describe the relevant medication error cases identified in the AERS search and discuss DMEPA’s evaluation of the proposed labels and labeling for Forfivo XL.

#### **3.1 WELLBUTRIN XL MEDICATION ERROR CASES**

Following the noted exclusions, we evaluated a total of nine cases (n=9) relevant to this review. The cases were classified according to the following medication error types:

- Extra dose (n=3): These cases involve the patient accidentally taking a second dose of Wellbutrin XL or generic after already taking the morning dose that day. The cases lacked detail as to the reasons for these errors. The patient in one case experienced confusion and was taken to the emergency room.
- Wrong technique (n=3): These cases involve the patient cutting or crushing the tablet prior to administration. The patient in one case was instructed by the prescriber to cut the tablets in half to reduce the dizziness she felt with the full 300 mg dose. However, no adverse effects were noted from taking the split tablet. Another patient split the tablet to make it easier to swallow but experienced hallucinations. The remaining patient crushed the tablet prior to swallowing but no cause or patient outcome were reported.
- Overdose (n=2): These cases involve the patient receiving a prescribed Wellbutrin XL dose of 600 mg daily. One patient experienced serotonin syndrome, a speech impediment and myoclonus on this dose. The other patient experienced seizure.
- Dose Omission (n=1): This case involves a missed dose of Wellbutrin XL due to a hospital admission for another concurrent medical condition. The dose was missed while the patient was in the emergency room, but continued after admission as an inpatient.

### **3.2 CONTAINER LABELS**

- The medication guide statement appears on the side panel of the label and is not prominently displayed per 21 CFR 208.24(d).
- The established name lacks required prominence as required by 21 CFR 201.10(g)(2).
- The strength presentation is not located directly following the proprietary and established names.
- Medication errors have resulted because prescribers and patients mistakenly believe these products can be cut. Since Forfivo XL is an extended-release formulation and available as unit-of-use (30 tablets), a caution regarding cutting or chewing the tablet should be included on the container label.

### **3.3 INSERT LABELING**

The Dosage and Administration Section of the insert labeling may be a source of confusion for healthcare providers. Forfivo XL is not appropriate for the initiation of bupropion therapy in naïve patients which is noted in the 2.1 Section of Dosage and Administration section of the inset labeling. However, sections 2.2 “Initial Treatment with Forfivo XL and 2.3 “Maintenance Treatment with Forfivo XL” lead healthcare providers to incorrectly believe that Forfivo XL may be used to initiate Bupropion therapy.

Additionally, the Dosage and Administration section as well as the Highlights of the insert labeling lack the actual dose of Forfivo XL as “one tablet by mouth daily.”

## **4 CONCLUSIONS AND RECOMMENDATIONS**

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors because of the lack of prominence of the medication guide statement and the clutter of the container label makes the other information difficult to read. We recommend the following:

- A. Container Label
  1. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
  2. Revise and relocate the strength presentation so that it appears directly below the established name. Include the unit of measure (mg) in the color field that highlights the numeric strength.
  3. If space permits, relocate the statement “Once daily” to the lower left corner of the principle display panel in line with the net quantity statement.

4. Relocate the Medication Guide statement to the principle display panel of the container label. In addition, the statement must state that the Medication Guide is attached or alternative how the dispenser is to obtain the document per 21 CFR 208.24(d).
5. Revise the usual dose statement to read, “Take one tablet daily. **Swallow tablets whole.** Do not cut, chew or crush.”
6. Delete the statement from the side panel “DO NOT USE if safety seal under cap is broken or missing” to provide space for the manufacturer statement and improve readability.

B. Insert Labeling – Comments to Division of Psychiatry Products

1. Revise the Dosage and Administration Section (including Highlights) to state the dose of Forfivo XL as “one tablet (450 mg) once daily.” (See Appendix C.)
2. DMEPA recommends removal of sections 2.2 and 2.3 in the Dosage and Administration section as the information on the titration of bupropion is included in Section 2.1 General Considerations. If these sections are included, we recommend the use of the phrase “Bupropion extended-release (once daily) tablets” to describe the product that can be used to initiate and to titrate doses of Bupropion to 300 mg daily.

If the Division has further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

**APPENDICES**

**Appendix A:** Container Labels – 30 count



(b) (4)

**Appendix B:** ISR numbers of retrieved AERS reports

7505274	7249955	7311869	7249796	7512573	7642275	7591892	7440559	7473209
7249906	7232556	7292653	7249903	7676638	7640766	7655551	7493640	7472529
7249912	7227149	7377658	7249933	7673691	7425844	7571519	7687826	7708760
7249927	7331655	7563440	7227103	7660102	7250935	7600526	7611242	7622373
7225485	7360827	7470123	7306113	7653739	7244662	7545861	7678013	7626142
7237208	7239174	7451291	7300770	7397133	7249640	7674805	7690139	7603278
7271522	7299361	7485502	7288602	7249896	7358169	7648927	7275914	7522410
7283744	7396402	7537446	7294040	7249941	7302095	7232389	7270744	
7286134	7472851	7542554	7294090	7249975	7292726	7249751	7275983	
7465651	7509826	7628228	7496759	7244660	7271604	7249815	7342820	
7491898	7679598	7669761	7406143	7369315	7298513	7249831	7455649	
7556663	7638605	7591425	7473211	7336150	7313149	7249874	7327832	
7542557	7438284	7625260	7546457	7283424	7410817	7249908	7339720	
7562157	7234097	7636274	7561257	7269343	7358851	7249913	7352839	
7529433	7249968	7646539	7706895	7385700	7456246	7250936	7380815	
7605993	7215512	7529436	7573853	7484355	7456247	7353408	7349668	
7705522	7328241	7529437	7642148	7622423	7440606	7397117	7249948	
7226413	7286050	7605596	7563379	7545828	7478922	7383558	7286438	
7249895	7271544	7244163	7625988	7562156	7466774	7383561	7235042	
7249949	7322880	7249784	7602667	7628267	7559221	7400190	7423743	

**Appendix C:** Edits to Highlights Section of the Insert labeling (Edits is red font)



(b) (4)

(b) (4)

**Appendix D:** Edits to Section 2 Dosage and Administration Section (Edits in red font)

(b) (4)

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/s/  
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RICHARD A ABATE  
10/12/2011

CAROL A HOLQUIST  
10/13/2011

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: October 5, 2011

TO: Thomas Laughren, M.D.  
Director, Division of Psychiatry Products  
Office of New Drugs

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Amended Review of EIR Covering NDA 22-497, FORFIVO XL  
(Bupropion Hydrochloride 450 mg Extended-Release)  
Tablet from IntelGenx, Corp., Quebec, Canada

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspection of clinical portion of the following study:

**BPOP0-520**: "Single Dose, randomized, three-way, three-period, three-treatment, crossover comparative Bioavailability Study of Bupropion Hydrochloride 450 mg Extended Release Tablets (1 x 450 mg) and Wellbutrin XL® 150 mg Extended Release Tablets (3 x 150 mg) in Healthy Male Volunteers under Fasting and Fed Conditions"

The inspection of clinical portion was conducted at **Cetero Research, 4801 Amber Valley Parkway, Fargo, ND**. Following the inspection at Cetero-Fargo (September 12-16, 2011), no Form FDA-483 was issued.

This amendment clarifies the reason for cancellation of the requested bioanalytical inspection at [REDACTED] (b) (4)  
[REDACTED] On September 29, 2011, DBGC requested cancellation of the inspection request, due to the following reasons:

- Resource and scheduling issues with ORA investigator will make it difficult to complete the inspection prior to the action goal date.
- This analytical site has been inspected several times over the past few years, with no serious observations. The last inspection was completed [REDACTED] (b) (4), and no Form 483 was issued.

The Office of Clinical Pharmacology (OCP) concurred with this cancellation on October 3, 2011.

**Conclusion:**

The clinical and bioanalytical data from this study are acceptable for your review. After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGCC, OSI

**Final Classification:**

**NAI - Cetero Research, Fargo, ND**  
FEI: 1720861

CANC - [REDACTED] (b) (4)

cc:  
OSI/Ball/Moreno  
OSI/DBGCC/Salewski/Dejernet/Matthews  
OSI/DBGCC/BB/Mada/Skelly/Haidar  
ODE1/DPP/Laughren/Ansah  
OCP/DCP1/Yu/Gobburu  
ORA/MIN-DO/Singh  
Draft: SRM 10/04/2011  
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SRIPAL R MADA  
10/05/2011

MICHAEL F SKELLY  
10/05/2011

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: October 3, 2011

TO: Thomas Laughren, M.D.  
Director, Division of Psychiatry Products  
Office of New Drugs

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-497, FORFIVO XL  
(Bupropion Hydrochloride 450 mg Extended-Release)  
Tablet from IntelGenx, Corp., Quebec, Canada

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspection of clinical portion of the following study:

**BPOP0-520**: "Single Dose, randomized, three-way, three-period, three-treatment, crossover comparative Bioavailability Study of Bupropion Hydrochloride 450 mg Extended Release Tablets (1 x 450 mg) and Wellbutrin XL<sup>®</sup> 150 mg Extended Release Tablets (3 x 150 mg) in Healthy Male Volunteers under Fasting and Fed Conditions"

The inspection of clinical portion was conducted at **Cetero Research, 4801 Amber Valley Parkway, Fargo, ND**. Following the inspection at Cetero-Fargo (September 12-16, 2011), no Form FDA-483 was issued.

The inspection of analytical portion was cancelled by Office of Clinical Pharmacology, dated on October 3, 2011, due to lack of serious observations based on DBGC's previous inspections.

Page 2 - ANDA 22-497, FORFIVO XL (Bupropion hydrochloride  
Extended-Release Tablet, 450 mg

**Conclusion:**

The clinical data are acceptable for your review. After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGC, OSI

**Final Classification:**

**NAI - Cetero Research, Fargo, ND**  
FEI: 1720861

cc:

OSI/Ball/Moreno

OSI/DBGC/Salewski/Dejernett/Matthews

OSI/DBGC/BB/Mada/Skelly/Haidar

ODE1/DPP/Laughren/Ansah

OCP/DCP1/Yu/Gobburu

ORA/MIN-DO/Singh

Draft: SRM 10/03/2011

Edit: MFS 10/03/2011

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FACTS: 1296950

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/s/  
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SRIPAL R MADA  
10/03/2011

MICHAEL F SKELLY  
10/03/2011  
Skelly signing on behalf of Dr. Haidar

# **REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW**

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 022497

**Name of Drug:** FORFIVO XL (bupropion hydrochloride 450 mg extended-release tablets)

**Applicant:** IntelGenx Corporation

## **Labeling Reviewed**

**Submission Date:** 05/4/11

**Receipt Date:** 05/13/11

## **Background and Summary Description**

The sponsor, IntelGenx Corp, has resubmitted (i.e. a class 2 Resubmission) their application to which we issued a complete Response on February 3, 2010. This application provides for a new higher strength formulation of bupropion [i.e. FORFIVO XL (bupropion hydrochloride 450 mg extended-release) tablets] for the treatment of Major Depressive Disorder. Currently, the highest dose available for the Extended-Release formulation is 300 mg.

## **Review**

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. Font size should be consistent throughout Highlights (HL), Table of Content (TOC), and Full Prescribing Information (FPI).

## **Conclusions/Recommendations**

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in an Advice Letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by September 7, 2011. The resubmitted

labeling will be used for further labeling discussions.

Kofi Ansah, Pharm.D.	08/18/11
Senior Regulatory Project Manager	Date
Paul David, R.Ph.	08/19/11
Chief, Project Management Staff	Date

## Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

### Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font. - *HL should be corrected so that Contraindications immediately follows Dosage Forms & Strength (i.e. currently it's on the next page).*
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. - *Need to limit HL to ½ page or request a waiver.*
- There is no redundancy of information. - *There is redundancy in HL (e.g. 5th bulleted item under Contraindications is redundant with 5th bulleted item under DI).*
- If a **Boxed Warning** is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC). - *Insert this horizontal line.*
- All headings must be presented in the center of a horizontal line, in **UPPER-CASE** letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (**FPI**) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading - if no contraindications are known, it must state "None")
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
    - *This shouldn't be merged with HL limitation statement -- Must be on a separate line and should read; FORFIVO XL (bupropion hydrochloride extended-release tablets), for oral use.*
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: **Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.** - *Not applicable in this case.*
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “**Dosage and Administration, Coronary Stenting (2.2) -- 2/2010.**”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”
- **Indications and Usage**
  - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
  - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
  - All contraindications listed in the FPI must also be listed in HL.
  - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction under FPI. - *Describe the type and nature of the adverse reaction under FPI*
  - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers. - *The # provided was (b) (4) (i.e. must be a toll-free # if this is not such).*
- **Patient Counseling Information Statement**
  - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).** - *This product has a Medication Guide (i.e. must use the appropriate format as shown).*
- **Revision Date**
  - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and bold type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI. - *Make corrections to 2.4* <sup>(b) (4)</sup>
- All section headings must be in bold type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**
  - A horizontal line must separate the TOC and FPI.
  - The heading - **FULL PRESCRIBING INFORMATION** - must appear at the beginning in UPPER CASE and bold type.
  - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - Must have a heading, in UPPER CASE, bold type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use bold type and lower-case letters for the text. - *Missing the word "WARNING" and the text should be in bold.*
  - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**

For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. - (i) <sup>(b) (4)</sup> -- *Must use AR consistently* (ii) *Subsection Heading* <sup>(b) (4)</sup> - *They should match.*

For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

This section is required and cannot be omitted.

Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

## Enclosure - (Sponsor’s 05-4-11 draft Labeling)

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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KOFI B ANSAH  
08/22/2011

PAUL A DAVID  
08/23/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: June 24, 2011

TO: Thomas Laughren, M.D.  
Director, Division of Psychiatry Products  
Office of Drug Evaluation

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-497, Bupropion HCl 450 mg ER tablets from Cary Pharmaceuticals, Inc.

At the request of Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGC) audited both clinical and analytical portions of the BE study # 3631, entitled "A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Bupropion HCl 450 mg ER tablets versus Wellbutrin XL<sup>®</sup> 150 mg Tablets in Normal, Healthy, Nonsmoking Male and Female Subjects" at [REDACTED] (b) (4)

DBGC sent the inspection summary memo for the above audit to DPP on November 10, 2009. DBGC received [REDACTED] (b) (4) response to the Form FDA-483 (see **Attachment 1**) on November 20, 2009 (dated November 19, 2009) soon after the inspection summary memo was forwarded to DPP.

**Conclusion:**

Following our evaluation of [REDACTED] (b) (4) response to the Form FDA-483, DBGC's recommendation to DPP in our November 10, 2009, EIR review remained unchanged.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGCC, OSI

**Final Classification:**

**Clinical and Analytical**

**VAI -** [REDACTED] (b) (4)

**FEI:** [REDACTED] (b) (4)

CC:  
OSI/Ball  
OSI/DBGCC/Mada/Yau/Haidar/Salewski/Dejernet/CF  
ODE1/DPP/Ansah/Laughren  
OCP/DCP1/Baweja/Yu  
HFR-CE450/Kondas  
Draft: SRM 06/24/2011  
Edit: MKY 06/24/2011  
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/s/  
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SRIPAL R MADA  
06/24/2011

MARTIN K YAU  
06/24/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: June 15, 2011

TO: Associate Director  
International Operations Drug Group  
Division of Foreign Field Investigations (DFFI)

Director, Investigations Branch  
Minneapolis District Office  
212 3<sup>rd</sup> Ave, South  
Minneapolis, MN 55401

From: Martin K. Yau, Ph.D. \_\_\_\_\_  
Acting Team Leader (Bioequivalence Branch)  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: FY 2011, **High Priority User Fee NDA, Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 22-497  
DRUG: FORFIVO XL (Bupropion hydrochloride  
Extended-Release Tablet, 450 mg  
SPONSOR: IntelGenx Corp.  
Saint-Laurent, Quebec, CANADA  
US AGENT CONTACT: Bethany J. Hills, Esq.,  
Hodgson Russ LLP  
Buffalo, NY  
TEL: (716) 848-1554

**This memo requests that you arrange for inspection of the clinical and analytical portions of the following bioequivalence study. An OSI (formerly DSI) scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact OSI upon receipt of this assignment to arrange scheduling of the inspection. The inspections should be completed before September 19, 2011.**

**Study Number:** BPO-P0-520

**Study Title:** "Single Dose, randomized, three-way, three-period, three-treatment, crossover comparative Bioavailability Study of Bupropion Hydrochloride 450 mg Extended Release Tablets (1 x 450 mg) and Wellbutrin XL® 150 mg Extended Release Tablets (3 x 150 mg) in Healthy Male Volunteers under Fasting and Fed Conditions"

**Clinical Site :** Cetero Research  
4801 Amber Valley Parkway  
Fargo, ND 58104  
TEL: (701) 239-4750

**Clinical Investigator:** Anthony R. Godfrey, Pharm. D.  
E-mail: anthony.godfrey@cetero.com

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firms. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings.

Please check the batch numbers of the test and reference products used in this study with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. The site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples

from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Samples of the test and reference products should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Court house and Custom house Bldg.  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator or the responsible person at the clinical investigator's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and shipped them to DPA under current program directives. Please see the IOM and/or contact your district or DFFI for assistance with the Sample Collection Report.

**Analytical Site:**

**Analytical  
Investigator:**

**Bioanalytical  
Contact:**

**Methodology:** LC-MS/MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be

Page 4 - BIMO Assignment, NDA 22497, FORFIVO XL (bupropion hydrochloride Extended Release Tablets, 450 mg

compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. **The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Michael F. Skelly, Ph.D.  
(301) 796-3375 (Foreign)

Jyoti B. Patel, Ph.D.  
(301-796-4617 (Domestic)

CC:

CDER DSI PM TRACK

OSI/DBGC/Haidar/Yau/Skelly/Patel/Dejernett/CF

HFC-130/ORA HQ DFFI IOB BIMO

HFR-CE850/Cheryl Bigham (DIB)

HFR-CE8590/Constance Richard-Math (BIMO)

OND/ODEI/DPP/Thomas Laughren/Kofi Ansah/Jing Zhang

OTS/OCP/DCPI/Bei Yu

OTS/OCP/DPM/Jogarao Gobburu

Draft: JBP 6/15/2011,

Edit: MKY 6/17/2011

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/s/  
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JYOTI B PATEL  
06/17/2011

MARTIN K YAU  
06/17/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 10, 2009

TO: Thomas Laughren, M.D.  
Director, Division of Psychiatry Products (DPP)  
Office of New Drugs (HFD-130)

FROM: Sripal R. Mada, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *Mart: K. Yan 11/10/09*  
Associate Director (Bioequivalence)  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-497, Bupropion HCl 450 mg ER tablets from Cary Pharmaceuticals, Inc.

At the request of Division of Psychiatry Products (DPP), the Division of Scientific Investigations (DSI) audited both clinical and analytical portions of the following bioequivalence (BE) study:

**Study # 3631:** "A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Bupropion HCl 450 mg ER tablets versus Wellbutrin XL<sup>®</sup> 150 mg Tablets in Normal, Healthy, Nonsmoking Male and Female Subjects"

Study #3631 was conducted by [redacted] (b)(4)  
at two research facilities in [redacted] (b)(4). The first  
facility is located at [redacted] (b)(4)  
and the second facility is located at [redacted] (b)(4)

[redacted]

Following the inspection (October 26-30, 2009), Form FDA-483 was issued (**Attachment 1**). The Form FDA-483 observations and DSI's evaluations are provided below.

**Analytical site:** [REDACTED] (b) (4)

**1. Failure to retain the study reserve samples (test product: Bupropion HCl 450 mg ER tablets; reference product: Wellbutrin XL 150 mg tablets) used in bioequivalence Study # 3631 as required by the regulations. The reserve samples were sent back to the study co-sponsor (IntelGenx Corp., Quebec, Canada).**

[REDACTED] (b) (4) fails to meet the regulatory requirements for retention of products used in bioavailability or bioequivalence study (21 CFR 320.38 and 320.63). Per the request of co-sponsor of this NDA, [REDACTED] (b) (4) shipped back all the reserve samples (see documents collected during the inspection in **Attachments 2, 3 and 4**).

As the test and reference products were not retained at the clinical study site, the authenticity of the products used in Study #3631 cannot be confirmed.

**2. Failure to perform sufficient assessments of Incurred Sample Reproducibility (ISR). Only 2.78% (39/1405) of bupropion and its metabolite samples were reanalyzed for ISR.**

As cited in the above 483 observation, the SOP for ISR at the time when the study was conducted was not adequate. However, [REDACTED] (b) (4) has now revised their SOP (effective January 2, 2009) to address the sample size issue by requiring [REDACTED] (b) (4) of study samples to be re-assayed. Moreover, a review of the ISR data obtained by [REDACTED] (b) (4) previously from 39 subject samples shows that the original and repeat data are similar, suggesting significant ISR problem is unlikely.

**3. Pipettes are calibrated only once every three months. There is no other procedure employed to check the accuracy of the pipettes during the entire three-month period, which would include the study period.**

Per the current SOP, the performance of pipettes will not be checked at anytime other than the calibration performed once in every 3 months. During the inspection close out meeting, [REDACTED] (b) (4) acknowledged this observation and agreed to revise the current SOP to address this issue.

4. Raw data sheets and the analytical study reports were not always documented correctly and/or accurately. For example:

- A. Corrections on raw data entry sheets were not signed and dated in several occasions.
- B. Failure to provide the reason for corrections/strike-outs in the data entry sheets.
- C. Hemolyzed samples were not mentioned or discussed in the analytical study reports, even though sample processing and study update records recorded a large number of hemolyzed study samples.

(b)(4) acknowledged their mistakes in raw data sheets and their failure to report the number of hemolyzed samples in the analytical report submitted to the FDA. DSI confirmed during the inspection that (b)(4) had conducted validation experiment using hemolyzed samples. The results showed that hemolyzed samples did not affect the precision and accuracy of the analytical method.

**Conclusion:**

The inspection at (b)(4) found that the regulatory requirements concerning retention of study products used in bioavailability or bioequivalence study were not followed (see 483 item 1). Consequently, the authenticity of the test and reference products tested in Study 3631 cannot be assured. The other findings (i.e., 483 items 2, 3 and 4) are not likely to affect the study outcomes.

Please note that DSI has not yet received the written response to the Form FDA-483 from (b)(4). DSI will update DPP if our review of the response upon receipt resulted in a change of our recommendation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



---

Sripal R. Mada, Ph.D.

**Final Classification:**

**Clinical and Analytical**

VAI - [REDACTED] (b) (4)

FEI: [REDACTED] (b) (4)

cc:

DSI/GLPBB/Mada/Kaufman/Rivera-Lopez/CF

ODE1/DPP/Ansah/Laughren

OCP/DCP1/Baweja/Yu

Draft: SRM 11/04/2009

Edit: MKY 11/05,09/2009

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FACTS: 1061165

Email:

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HFR-CE450/Kondas - Karen.Kondas@fda.hhs.gov

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

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/s/

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SRIPAL R MADA

11/10/2009

Dr. Yau (Acting for Dr. Viswanathan) signed the paper copy on 11/10/2009. Paper copies available on request. The scanned paper document has the original signature.