

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201152Orig1s000**

**OTHER REVIEW(S)**

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

**Division of Antiviral Products (DAVP)**

**Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)**

**Application: 201-152**

**Drug: Viramune<sup>®</sup> XR<sup>™</sup> (nevirapine) extended-release tablets**

## **Material Reviewed:**

Submission Date: March 15, 2011

Receipt Date: March 15, 2011

Submission Dates of Structured Product Labeling (SPL): June 03, 2010

## **Type of Labeling Reviewed:**

- Final agreed-upon labeling between FDA and BIPI on March 24, 2011 via electronic mail (Attachment 4).
- The last approved Medication Guide for NDAs 20-636/S-036 and 20-933/S-027, dated January 7, 2011.

## **Background and Summary:**

This original new drug application provides for the use of Viramune<sup>®</sup> XR<sup>™</sup> (nevirapine) extended-release 400 mg tablets, once daily, in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. This application also proposes modifications to the approved Viramune<sup>®</sup> (nevirapine) Tablets (NDA 20-636) and Oral Suspension (NDA 20-933) risk evaluation and mitigation strategy (REMS) by including Viramune<sup>®</sup> XR<sup>™</sup> (nevirapine) extended-release tablets.

Division of Drug Marketing, Advertising, and Communication (DDMAC), Division of Risk Management (DRISK), and Division of Medical Error Prevention and Analysis (DMEPA) were internally consulted for labeling review and recommendation. Recommended changes from these consults, as agreed by DAVP, were included in the labeling negotiated with BIPI.

## **I. Review of the Package Insert:**

A preliminary content and format review was completed on December 14, 2010 and deficiencies were noted (Attachment 1). During the labeling negotiation with BIPI, revisions were proposed to correct these deficiencies. BIPI agreed to these revisions. On March 17, 2011, a final content and format review of the package insert was found acceptable (Attachment 2). See Attachment 4 for the final package insert.

## **II. Review of the Medication Guide:**

Proposed modifications to the REMS include adding nevirapine (NVP) XR extended-release information to the Medication Guide last approved on January 7, 2011 for NVP immediate-release (IR) and oral suspension (OS) formulations. The intent of these modifications is to have all the nevirapine formulations (i.e. XR, IR, and OS) share one MG and REMS. Below is a detailed review of changes in the MG since January 7, 2011. Minor editorial edits will not be mentioned but is captured in Attachment 3.

1. The extended-release formulation was added in the beginning of the MG as follows:

**MEDICATION GUIDE**

**VIRAMUNE® (VIH-rah-mune)  
(nevirapine)  
Tablets**

**VIRAMUNE® (VIH-rah-mune)  
(nevirapine)  
Oral Suspension**

**VIRAMUNE® XR™ (VIH-rah-mune)  
(nevirapine)  
Extended-Release Tablets**

(b) (4)

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

Supervisory Comment/Concurrence:

*{See appended electronic signature page}*

Karen Winestock  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Attachments:

Attachment 1: Preliminary format and content review

Attachment 2: Final format and content review

Attachment 3: MG comparison of last approved (1/2011) to the final MG agreed on March 24, 2011.

Attachment 4: Final and clean USPI and MG

Drafted: Himaya 03/17/11 and 3/18/11

Revised/Initialed: Winestock eso 3/22/11

Finalized: 3/23/11

Filename:v: DAVP/CSO/Himaya/NDA/201152

## **Common Labeling Problems: Content and Format Requirements for Prescribing Information**

- Use this document as a check list. You can mark items that represent a discrepancy between the labeling requirement and the applicant-submitted prescribing information.
  - RPM Comment: This checklist was reviewed and completed by Amalia Himaya on 12/14/10. Discrepancies were found and noted below. These have been corrected in the final label.

### **General Information**

- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to the Table of Contents (TOC) and the Full Prescribing Information (FPI).
- Delete “Rx only” statement appearing anywhere in prescribing information. This statement is only required for container and carton labels.

### **Highlights (HL)**

- **General comments**

- A logo should not appear in HL. A small logo is allowed at the end of the FPI with manufacturer’s contact information.
- The HL must be limited in length to one-half page, in 8 point type, two-column format. (Waivers may be granted in unusual situations, but not until the end of the review cycle when it can be determined that a waiver is truly needed.)
  - RPM Comment: DAVP granted waiver for >1/2 page.
- 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.)
- There must be white space before each major heading.
- Use command language (e.g. “give” instead of “should be given”).
  - RPM Comment: Command language was applied consistently in the package insert.
- A horizontal line must separate the HL, TOC and FPI.

- **Highlights Limitation Statement**

- The highlights limitation statement must read as follows: “These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].”

- **Product Title**

The product title must include the drug names (proprietary and nonproprietary) followed by the drug's dosage form, route of administration (ROA), and, if applicable, controlled substance symbol. However, if the ROA is typical for the dosage form and is commonly understood (e.g., tablets or capsules), omit the ROA (for oral use).

- **Initial U.S. Approval**

Include the 4-digit year of the initial U.S. approval of the new molecular entity (NME), new biological product, or new combination of active ingredients. If this is a NME, the year will correspond to the current approval action.

- **Boxed Warning**

The boxed warning is a concise summary.

The boxed warning 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").

The boxed warning must have the verbatim statement "See full prescribing information for complete boxed warning."

- **Recent Major Changes (RMC) - N/A**

The RMC applies only to supplements and is limited to five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions.

For RMC, the heading and, if appropriate, subheading of each labeling section affected by the change must be listed together with each section's identifying number and the date (MM/YYYY format) on which the change was incorporated in labeling. The date will be the month/year that the supplement is approved. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010." Remember to update before approval.

For RMC, 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 in HL for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

A section or subsection that is removed should be noted as such in RMC. The text noting the change should include the title of the section/subsection removed, followed by the term, "removal" and date of removal. For example, Dosage and Administration, Subsection Title (2.X) --- removal XX/2010.

- **Indications and Usage**

If a product is a member of an established pharmacologic class the following statement must appear under the Indications and Usage heading in HL: "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

**n/a** If a pharmacologic class is not listed, an established pharmacologic class should be proposed. The pharmacologic class must be scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from HL.

Confirm the established pharmacologic class at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>

- **Dosage and Administration**

Avoid error-prone abbreviations, symbols and dose designations when describing dosage and administration information. Refer to the Institute of Safe Medication Practices' website at <http://www.ismp.org/Tools/abbreviationslist.pdf>.

➤ RPM Comment: This has been corrected during the labeling negotiation. The symbol ">" has been spelled out to "greater than."

- **Dosage Forms and Strengths**

Include strength, potency of dosage, and whether the product is scored. If the product is not scored, do not say "not scored."

Do not include "how supplied" information.

- **Contraindications**

Contraindications heading must be included in HL and not omitted. If there are no contraindications, you must state "None."

All contraindications listed in the FPI must also be listed in HL.

- **Warnings and Precautions**

List warnings and precautions in decreasing order of importance (i.e., reflecting the relative public health significance) regardless of drug class.

- **Adverse Reactions**

Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) should be included in Highlights. Other terms, such as "adverse events" or "treatment-emergent adverse events" which have no regulatory definition cannot be used.

Include criteria used to determine inclusion (e.g., incidence rate greater than X%)

Do not include "adverse events" from postmarketing experience.

For the adverse reactions reporting statement, a general customer service email address or a general link to a company website cannot be used. Delete this information if it appears in HL.

- **Drug Interactions**

This heading can be omitted. If included, must delineate specific instructions for preventing or managing drug interactions.

- **Use in Specific Populations**

This heading can be omitted.

Do not include the pregnancy category (e.g., A, B, C, D, X) in HL.

- **Patient Counseling Information Statement**

This heading is required and 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. For a new NDA, BLA, or supplement, the revision date will be the month/year of application or supplement approval. Remember to update before approval.

Do not include revision date at the end of the FPI. The revision date at the end of HL replaces the revision date at the end of the FPI and should not appear in both places. (Revision date may appear at the end of FDA-approved patient labeling.)

### **Contents: Table of Contents (TOC)**

The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning of the TOC in upper-case letters and bold type.

The headings and subheadings in the TOC must match the headings and subheadings in the FPI.

Do not use periods after the numbers for the section and subsection headings.

Because of SPL R4 requirements, do not list the Medication Guide (MG) or Patient Package Insert (PPI) in the TOC as a subsection heading under section 17.

In the TOC, section headings must be in bold type, and subsection headings must be indented and not bolded.

Create subsection headings that identify the content. Avoid using the words “General,” “Other” or “Miscellaneous” for a subsection heading.

Only section and subsection headings should appear in TOC. Headings within subsection must not be included.

When a 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)

When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the TOC. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: \*Sections or subsections omitted from the Full Prescribing Information are not listed.

## **Full Prescribing Information (FPI)**

- **General Format**

- The heading **FULL PRESCRIBING INFORMATION** – must appear at the beginning of the FPI in upper case letters and bold type.
- Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
- Do not use periods after the numbers for the section and subsection headings.
- Check that the section and subsection headings are named and numbered correctly as outlined under 21 CFR 201.56(d)(1).
- Use bold print sparingly since section and subsection headings in the FPI are required bolding. Use another method for emphasis such as italics or underline.
- The recommended presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, “[*see Use in Specific Populations (8.4)*]” not “See Pediatric Use (8.4)”. The cross-reference should be in brackets and italics. Do not use all capital letters or bold print.

- **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” which have no regulatory definition cannot be used.
- For Clinical Trials Experience subsection, the standard verbatim statement (or modification, if appropriate) should precede the presentation of adverse reactions from clinical trials:
  - “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.”

- RPM Comment: In the initial review of the label, (b) (4)  
This has since been corrected.

For Postmarketing Experience subsection, the standard verbatim statement (or modification, if appropriate) should precede the presentation of adverse reactions from spontaneous reports:

- “The following adverse reactions have been identified during post approval use of drug X. 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.

• **Clinical Pharmacology**

Include all pharmacokinetics (PK) information under subsection 12.3. Do not create another separate subsection heading for additional PK information (i.e., 12.6 Special Populations).

Since subsection 12.4 is reserved for “Microbiology” and 12.5 for “Pharmacogenomics,” do not use these subsection numbers for other subsection headings. If warranted, subsection 12.6 can be created for another PK topic that does not fit under the subsection headings 12.1 thru 12.5.

• **References N/A**

Include only references that are important to the prescriber.

Remove outdated references.

Ensure that references are cited in the FPI under the appropriate section/subsection.

Do not use a website link as a reference.

• **Patient Counseling Information**

Patient Counseling Information must follow after How Supplied/Storage and Handling section. This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient.

n/a When updating a label to the PLR format, this section must be developed if it does not exist in the old format.

Do not insert a PPI or MG in the Patient Counseling Information section in lieu of developing this section.

The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. The reference “[*See FDA-Approved Patient Labeling*]” or “[*See Medication Guide*]” should appear at the beginning of the Patient Counseling Information section to give it more prominence.

Since SPL Release 4 validation does not permit the inclusion of the MG as a subsection, the MG or PPI should not be a subsection under the Patient Counseling Information section but rather be included at the end of Section 17 without numbering as a subsection.

## **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.
- 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)
• <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.
  
- **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.

## 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).

### • 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)”

➤ RPM Comment: This checklist was reviewed and completed by Amalia Himaya on 3/17/11. No deficiencies noted.

31 Pages 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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AMALIA C HIMAYA  
03/24/2011

KAREN D WINESTOCK  
03/24/2011

**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:	March 2, 2011
Application Type/Number:	NDA 201152
To:	Debra Birnkrant, MD, Director Division of Antiviral Products
Through:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	L. Shenee' Toombs, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Viramune XR (Nevirapine) Extended-release Tablets 400 mg
Applicant/sponsor:	Boehringer Ingelheim
OSE RCM #:	2010-1339

## **1 INTRODUCTION**

This review evaluates the revised Viramune XR labels submitted on February 17, 2011, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed labels and labeling under OSE Review 2010-1339, dated February 2, 2011.

## **2 MATERIALS REVIEWED**

The Applicant provided revised label and labeling on February 17, 2011 (See Appendices A). We also reviewed the recommendations in OSE Review # 2010-1339.

## **3 DISCUSSION**

Review of the revised labels and labeling show that the Applicant implemented all of DMEPA's recommendations. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The revised labels and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

## 5 REFERENCES

OSE Review #2010-1339, Label and Labeling Review for Viramune XR (nevirapine) Extended-release tablets Toombs, L; February 2, 2011.

## 6 APPENDICES

### Appendix A: Container labels (30 count)

- Trade



- Sample



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/s/  
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LATOYA S TOOMBS  
03/02/2011

IRENE Z CHAN  
03/02/2011

CAROL A HOLQUIST  
03/02/2011

**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**

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**CLINICAL INSPECTION SUMMARY**

DATE: February 18, 2011

TO: Amalia Himaya, Regulatory Health Project Manager  
Peter Miele, M.D., Medical Officer  
Division of Antiviral Products

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 201-152

APPLICANT: Boehringer Ingelheim Pharmaceutical, Inc.

DRUG: Viramune XR (nevirapineXR)

NME: No.

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Naïve HIV-1 adult patients

CONSULTATION REQUEST DATE: July 28, 2010

DIVISION ACTION GOAL DATE: March 21, 2011

PDUFA DATE: April 3, 2011

## I. BACKGROUND:

The sponsor, Behringer Ingelheim Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for the use of Nevirapine (NVP) Extended release (Viramune) in the treatment of Naïve HIV-1 patients. Nevirapine, a dihydrodiazepinone, is a potent Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) with high therapeutic index.

Nevirapine is currently available on prescription, as a combination therapy for the antiviral treatment for HIV-1 infected patients with advanced or progressive immunodeficiency. The current nevirapine label recommends that patients initiate therapy with one 200 mg tablet of the immediate release tablet daily for the first 14 days (in combination with other antiretroviral agents) to lessen the frequency of rash followed by a one 200 mg tablet twice daily (in combination with antiretroviral agents). An extended release formulation of nevirapine may offer a meaningful therapeutic benefit, relative to marketed nevirapine by facilitating a once daily dosing regimen, thus improving treatment compliance. In addition, nevirapine extended release (XR) may demonstrate improved tolerability in comparison with the marketed product. The sponsor is seeking approval of 400 mg QD nevirapine XR formulation versus 200 mg BID nevirapine immediate release on a background of Truvada (emtricitabine and tenofovir DF) in treatment-naïve HIV-1 infected patients.

The Applicant has provided data from two studies, Study 1100.1526 and Study 1100.1486, in support of the approval of the new extended release dosage form. These studies are summarized in the following sections.

**Protocol 1100.1486, entitled: “A randomized, Double-Blind, Double-Dummy, Parallel Group, Active Controlled trial to Evaluate the Antiviral Efficacy of 400 mg QD Nevirapine Extended Release Formulation in Combination to 200 mg BID Nevirapine Immediate Release in Combination with Truvada in Antiretroviral Therapy Naïve HIV-1 Infected Patients (VERVE)”.**

Study 100.1486 assessed the safety and efficacy and the pharmacokinetics of NVP XR and NVP IR after 48 weeks of treatment.

In Study1100.1486, male and female subjects, over 18 years of age, were to be randomized to receive 400mg QD nevirapine extended release XR formulation or 200mg BID nevirapine IR, after a 14 day lead in period in which all the patients will receive 200 mg QD nevirapine IR formulation. Background antiretroviral therapy was to be Truvada (emtricitabine and tenofovir disoproxil fumarate) QD in both treatment groups. The treatment duration for the primary efficacy endpoint was 48 weeks. Subjects who completed the week 48 visit according to the protocol were allowed to enter an extension phase of the study to allow for the collection of long-term safety and efficacy data in a blinded manner.

The primary objective of this study was to evaluate the efficacy of 400mg QD nevirapine extended release formulation versus 200mg BID nevirapine immediate release in AVR therapy naïve HIV-1 patients after 48 weeks of treatment. Secondary objectives are to evaluate safety and pharmacokinetics of NVP ER and NVP IR.

The primary endpoint of this study was virologic response by week 48. Virologic response was defined as VL < 50 copies/mL prior to week 48 and without subsequent virologic rebound or change of AVR therapy prior to week 48. A virologic rebound was defined by two consecutive measurements of VL > 500 copies/mL, at least two weeks apart, after the measurement of VL < 50 copies/mL.

**Protocol 1100.1526, entitled: “An Open Label, Phase IIIb, Randomized Parallel Group Study to Assess the Efficacy and Safety of Switching HIV-1 Infected patients successfully Treated With a Nevirapine IR Based regimen to Niverapine XR 400 mg QD or remaining on Nevirapine IR 200 mg BID Based Regimen.”**

Study 1100.1526 assessed the safety and efficacy and the pharmacokinetics of NVP XR and NVP IR after 24 weeks of treatment.

In Study Protocol 1100.1526, male and female subjects, over 18 years of age, were randomized with a 2:1 allocation ratio to nevirapine NVPXR 400 mg QD or NVP IR 200 mg BID. Subjects remained on their previous background therapy. The treatment duration was to be 48 weeks. Subjects were to be switched to nevirapine XR after being on nevirapine immediate IR based regimen for at least 18 weeks. Efficacy, safety and pharmacokinetic (PK) parameters were evaluated at each visit.

The primary objective of this study was to demonstrate the efficacy of the nevirapine extended release (NVP XR) based regimen for HIV-1 infected patients who were receiving nevirapine immediate release (NVP IR) based regimen for at least 18 prior weeks of therapy. The secondary objective of this study is to assess the safety and tolerance of the NVP XR based regimen for HIV-1 infected patients who were receiving NVP IR regimen for at least 18 prior weeks of therapy.

The primary endpoint was the proportion of subjects with sustained virologic response (VL < 50 copies/mL) through week 24. The time window of week 24 is defined as 24 plus or minus 4 weeks from Day 1.

The review division requested inspection of six clinical investigators for the two study protocols (5 sites; 4 foreign sites and 1 domestic site to cover Study 1100.1486 and 1 domestic site to cover Study 1100.1526) as data from the two protocols are considered essential to the approval process. Four foreign clinical investigators and two domestic investigators were chosen for inspection of the two protocols. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, 2) site specific protocol violations, and 3) limited experience with this drug has been at foreign sites. Boehringer Ingelheim Pharmaceutical, Inc. is the Sponsor of this application.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Douglas Ward, M.D. Dupont Circle Physicians Group 1737 20 <sup>th</sup> Street, NW Washington, DC 20009 Site# 1001	Protocol 1526 Number of subjects listed 37	9/14-20/10	NAI
Josep Mallolas, M.D. Hospital Clinico y Pronvincial de Barcelona Servicio de enfermedades infecciosas/villarroel, 170 08036 Barcelona Site# 3401	Protocol 1486 Number of subjects listed 28	12/13-15/10	Pending  Preliminary: NAI
Pere Domingo, M.D. Hospital de la Santa Creu I Saint Pau Servicio de Enfermedades Infecciosas Avda. Saint Antoi Maria Claret 167 08025 Barcelona Site# 3410	Protocol 1486 Number of subjects listed 15	12/20-23/10	Pending  Preliminary: NAI
Mark Nelson, M.D. Vhelsea& Westminister Hospital At. Stephen's AIDS Trust 1st Floor, St. Stephen Centre 396 Fulham Road SW 109 (NH London) Site# 4403	Protocol 1486 Number of subjects listed 35	11/1-5/10	Pending  Preliminary: VAI
Johannes Bogner, M.D. Klinikum der Ludwigmaxmillians Universitat Medizinische Poliklinik Munchen Petttenkofenstrabe 8a 80336 Munchen Site# 4904	Protocol 1486 Number of subjects listed 7	9/22-10/8/10	Pending Preliminary :VAI
Steven Santiago, M.D. Care Resource Suite 300 3510 Biscayne Boulv. Miami, FL 33137 Sites# 0012	Protocol 1486 Number of subjects listed 34	9/13-10/1/10	Pending  Preliminary: VAI

Key to Classifications

NAI No deviations

VAI Deviation(s) from regulations

OAI Significant deviations for regulations. Data unreliable.

Pending Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

**Note: Observations noted below for 4 sites are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

Protocol Study 1526

1. **Douglas Ward, M.D.**  
**Washington, DC**

**a. What Was Inspected:** At this site, a total of 43 subjects were screened, six subjects were reported as screen failures. Thirty seven (37) subjects were randomized and 4 subjects terminated early. The remaining 33 subjects completed the study and are currently enrolled in the long term phase of the study. There were no deaths and no under-reporting of adverse events. Review of Informed Consent Documents for 25 subjects records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 25 random subjects were reviewed, including drug accountability records, vital signs, laboratory test results, IRB records, use of concomitant medications; source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

**b. General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Ward. The medical records reviewed were found to be in order and the data verifiable. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

**c. Assessment of Data Integrity:** The data, in support of clinical efficacy and safety at Dr. Ward's site are considered reliable and appear acceptable in support of the pending application.

Protocol Study1486

2. **Josep Mallolas, M.D.**  
**Bacelona, Spain**

**a. What Was Inspected:** At this site, a total of 28 subjects were screened and ten (10) subjects were reported as screen failures. Seven subjects were discontinued and the reasons were documented. Eighteen (18) subjects were randomized and completed the study. Twelve subjects opted to continue on the long term phase of the study. There were no deaths and no under-reporting of adverse events (exceptions noted below). Review of the Informed Consent Documents, for all subjects reviewed, verified that

subjects signed consent forms prior to enrollment. The subjects who continued on the long term treatment were all re-consented.

The medical records/source data for subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, and source documents were compared to e-CRFs and data listings for primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued; however, an issue identified with respect to not reporting elevated creatinine kinase (CK) levels was discussed at the site. Elevated CK levels were not reported as adverse events for at least four subjects randomized to the IR arm (12236, 12338, 12244 and 12251; CK levels of 1919, 698, 6890 and 2146(V8) and 3779 (V9) U/L respectively). The clinical investigators stated that the increase in CK levels in their medical judgment was due to exercise and were not considered as adverse events. However, the inspection team stressed the fact that exercise may elevate the CK levels, but not 9-20 times the upper limit of normal. In addition, the FDA inspection team recommended that in the future a comment should be made to address the clinical significance of the elevated levels. The review division medical team was notified of the finding with respect to increased CK levels. The Team Leader for safety was asked whether the increased levels of CK should be reported as adverse events. The response was that these should not have been reported as AEs even if the values are 9-20 X the upper limit of normal, as subjects did not complain of symptoms such as (body aches, weakness and change in urine color). Elevated CK levels in the absence of clinical symptoms are not considered clinically important events, and CK elevations of this magnitude may occur as a result of strenuous activities. No Form FDA 483 was issued to Dr. Mallolas.

The clinical investigators acknowledged the inspectional findings and promised to exercise more care in commenting to laboratory abnormalities in their future studies. The inspectional team was not convinced that the elevated CK levels were due to exercise only.

**c. Assessment of Data Integrity**

Although minor regulatory violations were noted, the findings are not likely to affect data integrity. However, the review division was informed of the findings and promised to follow-up with sponsor to explain the reasons for the elevated CK levels and will consider the impact in their assessment of safety or efficacy. The team concluded that the elevated CK levels may be due to exercise activities and not as an adverse event. The study appears to have been conducted adequately and the submitted by the sponsor may be used in support of the pending application.

**3. Pere Domingo, M.D.  
Barcelona, Spain**

**a. What Was Inspected:** At this site, a total of 15 subjects were screened, 7 subjects were reported as screen failures (for not meeting inclusion criteria), 8 subjects were randomized into the study, 3 subjects were discontinued and the reasons were

documented and (2 subjects were relocated). Three (3) subjects completed the study and re-consented to enroll in the long term phase of the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria use of concomitant medications; source documents for subjects were compared to case report forms (e-CRFs) and data listings, to include primary efficacy endpoints and adverse events and no discrepancies were noted.

**b. General Observations/Commentary:** At the conclusion of the inspection, No Form FDA 483 was issued to Dr. Domingo. However, our investigation found that Subject 12557 randomized to the IR arm experienced an elevation of Creatine Kinase (CK) of 4335U/L and no comment was made by clinical investigator regarding the clinical significance of the increased level; the clinical investigator stated that it is due to exercise activity and not drug related and is not considered an adverse event. The team provided the clinical investigator the CK value and asked the clinical investigator if 20 times the upper limit of normal is simply due to exercise and added that this may be considered as an adverse event. (The review division Team Leader for safety in the review division was informed about this as well, and DSI was provided the same comment as stated above).

The clinical investigator acknowledged the inspectional finding and verbally stated in the future will exercise more care in reporting adverse events in his future studies. Although he acknowledged the observation, the inspection team was not convinced that the CK level was simply due to exercise.

**c. Assessment of Data Integrity:** The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data (exception CK value for Subject 12557). In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection. The data generated from Dr. Domingo's site are considered reliable and appear acceptable in support of the application.

#### **4. Mark Nelson, M.D. London, UK**

**a. What was Inspected:** At this site, a total of 35 subjects were screened, 13 subjects were reported as screen failures, 16 subjects were randomized and 9 subjects completed the study. Eight (8) subjects were discontinued from the study and the reasons were documented. Review of Informed Consent Documents, for 18 subjects reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for 12 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, diary cards, IRB files, prior and current medications, inclusion/exclusion criteria, the use of concomitant medications; source documents for 12 selected subjects were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, a two item Form FDA 483 was issued to Dr. Nelson. Our investigation found protocol deviations.

**Protocol Violations:**

- The site did not use the most recent revised informed consent Version #6. The clinical investigator used Version # 5 instead by error. The clinical investigator agreed with the observation and stated that the error did not compromise the patient's safety. The clinical investigator re-consented the subjects with the correct version at a later point in time.
- The adverse events section (8.4.1) of the protocol states that all adverse events, serious and non-serious, will be fully documented on the appropriate CRF/eCRF. For example, Subject 13984 reported cold symptoms (cough, sore throat and rhinorrhea) on 12/3/08. These adverse events were not reported on the eCRF.
- The concomitant therapy section (4.2) of the protocol states all concomitant medication should documented in the eCRF. The protocol was not followed in that :

Subject 13961 received Piriton for itchy hands, and the use of Piriton was not reported on the eCRF concomitant therapy section. In addition, the subject received/used ibuprofen gel for painful muscles, and the use of ibuprofen was not recorded on the e-CRF.

The clinical investigator acknowledged the observations noted above in a written response dated November 15, 2010, in which the clinical investigator promised corrective action plan.

The medical records reviewed disclosed no other adverse findings that would negatively on the reliability of the data. With the exception of the items noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection. DSI finds his response acceptable.

**c. Assessment of Data Integrity:** Although regulatory violations were noted, the findings are considered isolated in nature and/or unlikely to significantly impact data reliability. The data from Dr. Nelson's site are considered reliable and appear acceptable in support of the pending application.

**5. Johannes R. Bogner  
Munich, Germany**

- a. **What was Inspected:** At this site, a total of 28 subjects were screened, and 9 subjects were reported as screen failures. Nineteen (19) subjects were randomized and 18 subjects completed the study. There were no deaths and no under-reporting of adverse events. Two subjects experienced adverse events which were accurately reported to the sponsor. Subject 10937 experienced a rupture of the supraspinatus tendon, and Subject 10946 developed Synovial Plica Syndrome during the study. Review of Informed Consent Documents for all records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 11 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, IRB records, use of concomitant medications; source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

- b. **General Observations/Commentary:** At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Bogner. Our investigation found protocol violations.

**Protocol Violations:**

The concomitant therapy section (4.2) of the protocol states that all concomitant medication should be documented in the eCRF. The protocol was not followed in that:

- Subject 10935 received an M-M RvaxPro vaccination and Menjugate Kit vaccination. These vaccinations were recorded in the eCRF.
- Subject 10935 received snake venom therapy for pain caused by Herpes Zoster. The use of snake venom was not reported in the eCRF.
- Subject 10948 received Novalgine and Talvosel in forte. These concomitant medications were not reported in the eCRF.
- Subject 10953 received Jodthyrox routinely for iodine deficiency. The use of Jodthyrox was not recorded in the eCRF.

The clinical investigator acknowledged the observations in a written response (not dated) and promised to ensure that the findings noted above will not recur in any future studies. DSI finds his action plan to be acceptable.

The medical documents reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be organized and the data verifiable. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** Although regulatory violations were noted, the findings are considered isolated in nature and /or unlikely to significantly impact data reliability. The data generated from this site are reliable and can be used in support of the pending application/indication.

**6. Steven Santiago, M.D.  
Miami, FL**

**a. What was Inspected:** At this site, a total of 33 subjects were screened and nine (9) subjects were reported as screen failures or withdrew consent prior to randomization. Eight subjects were terminated early. Twenty four (24) subjects were enrolled and 17 subjects completed the study. There was one death adequately reported to the sponsor, however, the IRB was notified at a later date. Review of the Informed consent Documents, for all subjects reviewed, verified that subjects signed consent forma prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 14 subjects were reviewed in depth, including drug accountability records, inclusion/exclusion criteria, vital signs, laboratory test results, IRB records, use of concomitant medications; source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

**b. General Observations/Comments:** At the conclusion of the inspection, a four item Form FDA 483 was issued to Dr. Santiago. Our investigation found protocol deviations and inadequate record keeping.

**Protocol Violations:**

1. According to the protocol, the clinical investigator must submit serious adverse events to the IRB within three (3) business days after they have knowledge of a serious adverse event. Subject 14349 died on (b) (6) from hypertensive condition and arteriosclerotic cardiovascular disease. The sponsor was notified one day after the site became aware of the death. However, the IRB was not notified till 11/25 /08.
2. According to the protocol Section 3.3.1 under inclusion criteria, patients had to meet certain criteria to be eligible for participation in the study. Subject 17546, an HIV-1 patient, had no Western Blot done to confirm positive serology for inclusion. In addition, Karnofsky scores could not be located for Subjects 14351, 17556 and 17550.
3. According to the protocol Appendix 10.3 Ketoconazole is not permitted to be used in combination with nevirapine during the study. The following subjects were treated with ketoconazole cream: Subjects 17549, 17546, 17550, 14356 and 14364.
4. Subject 14364's source document revealed that the screening visit was conducted on 3/13/08. However, the medical records revealed that the EKG on file for this visit was performed on 3/4/08. No waiver was found on site to allow for an EKG to be done prior to the screening.

**Record Keeping Violations:**

Review of source documents revealed that adverse events were not always reported to the sponsor via electronic case report forms (eCRFs) as follows:

- Subject 14353 experienced hemorrhoids at Visit 15;
- Subject 14364 experienced ulcer at Visit 5;
- Subject 17556 experienced neoplasm at Visit 5; and
- Subject 14349 experienced renal insufficiency at Visit 6, Upper respiratory infection at Visit 7 and nausea at Visit 2.

The clinical investigator acknowledged the inspectional findings in a written response dated October 25, 2010, in which he stated that all possible corrective and preventive measures will be taken to avoid such deviations from occurring in future studies.

**c. Assessment of Data Integrity:** Although regulatory violations were noted, the findings are unlikely to affect data integrity due to a small number of subjects involved. However, the review division may choose to consider excluding few subjects based on the findings above with respect to protocol violations in their assessment of efficacy or safety.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Six clinical investigator sites, two domestic and four foreign sites were inspected in support of this application. The inspections of Drs. Ward, Mollalas, Domingo, Nelson, Bogner and Santiago revealed no significant problems that would adversely impact data acceptability. Except for the noted observations at the selected site (Santiago), overall the data submitted from these sites are acceptable in support of the pending application.

**Note: Observations noted above for at least 4 inspections are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
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CONCURRENCE:

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANTOINE N EL HAGE  
02/23/2011

TEJASHRI S PUROHIT-SHETH  
02/23/2011

**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:	February 2, 2011
Application Type/Number:	NDA 201152
To:	Debra Birnkrant, MD, Director Division of Antiviral Products
Through:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	L. Shenee' Toombs, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Viramune XR (Nevirapine) Extended-release Tablets 400 mg
Applicant/sponsor:	Boehringer Ingelheim
OSE RCM #:	2010-1339

## **1 INTRODUCTION**

This review evaluates Boehringer Ingelheim’s proposed labels and labeling for Viramune XR from a medication error perspective.

## **2 METHODS AND MATERIALS**

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)<sup>1</sup>, principals of human factors, and lessons learned from postmarketing experience in our evaluation of labels and labeling of drug products. We also searched the FDA Adverse Event Reporting System (AERS) Database to determine if any medication errors due to labels and labeling have occurred with the existing marketed product, Viramune.

### **2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES**

A search of the AERS database was conducted on July 29, 2010 using the High Level Group Terms (HGLT) ‘Medication Errors’, and ‘Product Quality Issues’, with the search criteria active ingredients “nevirapine” trade name “Viramune” and verbatim substance search “Viram%”. No date limitations were set.

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 labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis.

### **2.2 LABELS AND LABELING**

This review focuses on the labels and labeling submitted on June 3, 2010 (see Appendix A) and the insert labeling submitted January 6, 2011 (no image).

## **3 RESULTS AND DISCUSSION**

The following section describes the findings and analysis of AERS cases and the labels and labeling reviewed.

### **3.1 ADVERSE EVENTS REPORTING SYSTEM SEARCH RESULTS**

The AERS search conducted on July 29, 2010 yielded 113 cases (see Appendix C for ISR numbers). Of these cases, 112 were excluded from further evaluation for the reasons outlined in Section 2.1 above (see Appendix B). The remaining case was considered relevant to this review and was categorized as a wrong drug error.

#### ***3.1.1 Wrong Drug due to packaging (n 1)***

We received one case in 1997 of a wrong drug error where a physician ordered Viracept but Viramune was dispensed. The reporter indicated both products are unit-dosed in similar color packaging, have similar spelling of trade and established names, and were shelved next to each other. The error was caught before reaching the patient.

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

Upon review of the currently marketed labels and labeling of Viramune and Viracept, DMEPA finds the labels and labeling adequately differentiated and no regulatory action is needed at this time.

### **3.2 LABELS AND LABELING**

It was determined that the labels and labeling need improvement in the following areas: ensuring commensurate prominence of the established name with the proprietary name and eliminating partial dosage information. Our recommendations are further explained in Section 4.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

Our evaluation noted areas where information on the carton and container labels and labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1, Comments to the Division. Section 4.2 (Comments to the Applicant) contains our recommendations to the Applicant for changes to the container labels. We request these recommendations be communicated to the Applicant.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

### **4.1 COMMENTS TO THE DIVISION**

#### **A. General Comments**

DMEPA notes the use of “immediate-release”, portrayed throughout the insert labeling, looks like the finalized dosage form; however we question the appropriateness of the use of this descriptor. DMEPA defers to CMC to make a determination regarding this concern.

#### **B. Dosage and Administration-Adults (2.1)**

1. Include a heading such as “Patients not currently taking immediate-release Viramune” for the dosing initiation instructions for patients who are not currently on nevirapine therapy. Providing a heading will clearly differentiate the two regimens for patients not currently on nevirapine therapy and treatment experienced patients. Additionally modify the heading, (b) (4) to “Switching patients from immediate-release tablets to Viramune XR tablets”. For consistency, include the section headers in the Dosage and Administration section of the highlights of prescribing information.
2. Modify the statement, (b) (4) to read, “Patients should swallow Viramune XR tablets whole. They should not be chewed, crushed or divided.”

#### **C. Patient Counseling Information-Administration (17.2)**

Include the statement, “Instruct patients to swallow Viramune XR tablets whole. They should not be chewed, crushed or divided.”

## 4.2 COMMENTS TO THE APPLICANT

### Container Labels (30 count) Trade/Sample

1. The entire established name is '(Nevirapine) Extended-release Tablets'. As currently presented 'Extended-release Tablets' has a greater prominence due to the font size. Modify the presentation of the established name so that '(nevirapine)' and 'Extended-release Tablets' have equal prominence. Additionally, ensure that the established name is at least ½ the size of the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. Delete the (b) (4) located on the principal display panel. (b) (4)
3. Per 21 CFR 208.24, modify the medication guide statement, (b) (4) to include how the medication guide is provided. For example, the statement could read "Pharmacist: Dispense with attached Medication Guide to each patient". (b) (4)  
Change the font to a color that increases the contrast with the white background.
4. Minimize the prominence of the company name 'Boehringer Ingelheim' and accompanying graphic. As currently presented it distracts from more important information on the principal display panel.
5. Increase the prominence of the product code segment (0597-**0123**-30) of the NDC number located at the top of the principal display panel. Additionally, decrease the prominence of the net quantity statement.
6. De-bold and minimize the "Rx Only" statement on the principal display panel.

**Appendix A: Container Labels (30 count)**

- **Trade**



(b) (4)

- **Sample**



(b) (4)

## **Appendix B: Excluded AERS search results**

The AERS search conducted on July 29, 2010, yielded 113 cases. Of these cases, 112 were excluded from further evaluation for the reasons below:

- Name confusion not due to labels and labeling (n=10)
- Medication error not related to Nevirapine (n=17)
- Intentional overdose (n=27)
- Overdose. Causality not determined; however, we reviewed the Dosage and Administration section of the insert labeling of Viramune to ensure the information is clear and not misleading. DMEPA determined the Dosage and Administration section is clear and not misleading. (n=19)
- Drug exposure during breastfeeding (n=13)
- Adverse Drug Reactions not related to medication errors (n=5)
- Dose omission errors due to non-compliant patient (n=11)
- Wrong frequency errors not due to labels and labeling (n=2)
- Wrong time of administration not due to labels and labeling. Patient did not follow study protocol. (n=1)
- Wrong patient error where one patient intentionally took another patient's medicine (n=1)
- Drug interaction error; however, interaction is already labeled (n=3)
- Drug monitoring error not relevant to this review (n=2)
- Wrong Technique error. Intramuscular administration of an oral suspension made from crushing a tablet mixing in sterile water. A review of the insert labeling shows instructions for compounding oral solutions (slurry) from oral tablets is not presented in the insert labeling, therefore DMEPA finds this technique inappropriate. However, since there is only one case, describing this technique DMEPA does not recommend regulatory action at this time. (n=1)

**Appendix C: AERS search results**

1. ISR 4161233-5 (relevant)	41. ISR 3571590-6	81. ISR 4861590-8
2. ISR 4209410-9	42. ISR 3503134-9	82. ISR 4050063-0
3. ISR 4168407-8	43. ISR 3391822-7	83. ISR 3244421-1
4. ISR 4114935-0	44. ISR 4177753-3	84. ISR 3493073-4
5. ISR 3009271-X	45. ISR 4038217-0	85. ISR 3397935-8
6. ISR 3021843-5	46. ISR 3456122-5	86. ISR 3918410-5
7. ISR 4009007-X	47. ISR 3275383-9	87. ISR 3193850-3
8. ISR 5391641-6	48. ISR 3265666-0	88. ISR 6643672-3
9. ISR 5384631-0	49. ISR 3239964-0	89. ISR 6347809-5
10. ISR 6504511-4	50. ISR 5878068-5	90. ISR 5253817-8
11. ISR 6547340-8	51. ISR 3403008-8	91. ISR 5563132-0
12. ISR 4832328-5	52. ISR 3246986-2	92. ISR 5639417-6
13. ISR 5675359-8	53. ISR 3642871-2	93. ISR 3066397-2
14. ISR 5903562-8	54. ISR 3820562-2	94. ISR 1977244
15. ISR 3772182-6	55. ISR 4335422-0	95. ISR 3688660-4
16. ISR 3065908-0	56. ISR 4156416-4	96. ISR 5322957-7
17. ISR 4610118-6	57. ISR 5977963-6	97. ISR 3714595-4
18. ISR 6681589-9	58. ISR 5264160-5	98. ISR 3242972-7
19. ISR 6082933-6	59. ISR 5655945-1	99. ISR 5191731-7
20. ISR 5136360-6	60. ISR 6637849-0	100. ISR 5195670-7
21. ISR 5134981-8	61. ISR 4731164-8	101. ISR 3514512-6
22. ISR 5098755-9	62. ISR 3789510-8	102. ISR 5614583-7
23. ISR 6395796-6	63. ISR 5853162-3	103. ISR 5333191-9
24. ISR 4335493-1	64. ISR 4146883-4	104. ISR 6505713-3
25. ISR 4999895-2	65. ISR 6209349-3	105. ISR 4865533-2
26. ISR 6264855-0	66. ISR 4964563-X	106. ISR 4757686-1
27. ISR 6246313-2	67. ISR 4649148-7	107. ISR 4865532-0
28. ISR 3222903-6	68. ISR 5752874-X	108. ISR 4868383-6
29. ISR 3345173-7	69. ISR 4437882-3	109. ISR 4868400-3
30. ISR 3199789-1	70. ISR 3498994-4	110. ISR 4870704-5
31. ISR 4092197-0	71. ISR 5732251-8	111. ISR 6080984-9
32. ISR 3126390-8	72. ISR 3141109-2	112. ISR 4945942-3
33. ISR 4121652-6	73. ISR 3641472-X	113. ISR 4945943-5
34. ISR 3985874-0	74. ISR 6633355-8	
35. ISR 3358232-X	75. ISR 6429039-1	
36. ISR 3416741-9	76. ISR 6263291-0	
37. ISR 6313777-5	77. ISR 5649736-5	
38. ISR 4754570-4	78. ISR 3933997-4	
39. ISR 5113594-8	79. ISR 6505716-9	
40. ISR 4238601-69	80. ISR 6505714-5	

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APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LATOYA S TOOMBS  
02/03/2011

IRENE Z CHAN  
02/03/2011

CAROL A HOLQUIST  
02/03/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** January 24, 2011

**To:** Amalia Himaya – Regulatory Health Project Manager  
Division of Antiviral Products (DAVP)

**From:** Lynn Panholzer, PharmD – Regulatory Review Officer  
Michelle Safarik, PA-C – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** DDMAC labeling comments for Viramune XR (nevirapine)  
extended-release tablets (Viramune XR)  
NDA 201152

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As requested in your consult dated June 24, 2010, DDMAC has reviewed the proposed product labeling (package insert (PI) and medication guide (med guide)) for Viramune XR.

DDMAC provided comments via e-mail on January 14, 2011, on a working version of the proposed PI that was marked-up and considered substantially complete by DAVP. DDMAC's e-mailed comments on the proposed PI are reiterated below in the attached clean copy.

DDMAC's comments on the proposed med guide are based on the substantially complete marked-up version of the revised proposed PI sent to DDMAC by DAVP via e-mail on January 21, 2011. Our comments are provided directly in the attached clean copy of the proposed med guide.

If you have any questions about DDMAC's comments on the proposed PI, please contact Lynn Panholzer at 301-796-0616 or at [lynn.panholzer@fda.hhs.gov](mailto:lynn.panholzer@fda.hhs.gov). If you have any questions about DDMAC's comments on the proposed med guide, please contact Michelle Safarik at 301-796-0620 or at [michelle.safarik@fda.hhs.gov](mailto:michelle.safarik@fda.hhs.gov).

29 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE L SAFARIK  
01/24/2011

LYNN M PANHOLZER  
01/24/2011

**RPM FILING REVIEW**  
**(Including Memo of Filing Meeting)**

**To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)**

<b>Application Information</b>		
NDA # 201152 (original) BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Viramune® XR™ Established/Proper Name: nevirapine Dosage Form: extended-release tablet Strengths: 400 mg		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) Agent for Applicant (if applicable):		
Date of Application: June 3, 2010 Date of Receipt: June 3, 2010 Date clock started after UN:		
PDUFA Goal Date: April 3, 2011	Action Goal Date (if different):	
Filing Date: August 2, 2010	Date of Filing Meeting: July 13, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): For use in combination with other antiretroviral agents for the treatment of HIV-1 infection.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>            and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): INDs 74,744 AND 36,026				
<b>Goal Dates/Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	XX			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		XX		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b>  <b>If yes, please list below:</b>																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5 year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3 year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b>			XX																	
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	XX			3 years																

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		XX		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ? <b>If not</b> , explain (e.g., waiver granted).	XX			
<b>Index</b> : Does the submission contain an accurate comprehensive index?	XX			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	XX			
<b>Controlled substance/Product with abuse potential</b> : Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>			XX	
<b>BLAs only</b> : Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #				

<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature?  <i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i>	XX			
Are all establishments and their registration numbers listed on the form/attached to the form?	XX			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a?	XX			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?  <i>Forms must be signed by the APPLICANT, not an Agent.</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	XX			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	XX			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature? ( <i>Certification is not required for supplements if submitted in the original application</i> )  <i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	XX			

<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	XX			
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		XX		
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	XX			
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	XX			
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		XX		

<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	XX			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	XX			
Is the PI submitted in PLR format?	XX			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	XX			
REMS consulted to OSE/DRISK?	XX			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	XX			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		XX		

<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		XX		This was scheduled on 9/24/07; however, BIPI cancelled this meeting after receiving FDA's preliminary comments.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>	XX			10/19/09
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		XX		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 13, 2010

**BLA/NDA/Supp #:** 201-152

**PROPRIETARY NAME:** Viramune® XR™

**ESTABLISHED/PROPER NAME:** nevirapine

**DOSAGE FORM/STRENGTH:** extended-release tablets, 400mg

**APPLICANT:** Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** For use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

**BACKGROUND:** Boehringer Ingelheim (BI) submitted a new drug application for nevirapine extended release tablets, a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for the treatment of HIV-1 infection in adults. Currently, Viramune® (nevirapine) tablets and suspension are commercially available in the United States with twice daily administration. For dosing convenience, the nevirapine extended release tablet formulation is being developed for once daily administration.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amalia Himaya	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Y
Clinical	Reviewer:	Peter Miele	Y
	TL:	Linda Lewis	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Lalji Mishra	Y
	TL:	Jules O'Rear	N
Clinical Pharmacology	Reviewer:	Vikram Arya	N
	TL:	Sarah Robertson	Y
Biostatistics	Reviewer:	Susan Zhou and Lan Zeng	Y
	TL:	Greg Soon	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pritam (Pete) Verma	Y
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Shrikant (Suresh) Pagay Sandra Suarez	N Y
	TL:	Steve Miller	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton, and container)	Reviewer:	Latoya Sheneé Toombs	Y
	TL:	Carlos Mena-Grillasca	Y
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	Y
	TL:	Claudia Karwoski	N
Bioresearch Monitoring (DSI)	Reviewer:	Antoine (Tony) El Hage	Y

	TL:	Tejashri Purohit-Sheth	
Other reviewers: OSE	Twanda Scales, RPM Kelly Cao, DPVII Team Leader		Y Y
Other attendees	Matt Bacho, PMHS Marcus Kendall, DAVP DD Safety		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> None</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<i>disease</i>	
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

**Comments:** CMC plan to send comments to BIPI before the 74-day letter is issued.

Review issues for 74-day letter

<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs/BLA supplements only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

### REGULATORY PROJECT MANAGEMENT

**Signatory Authority:** Jeffrey Murray, M.D., MPH, Deputy Director

**21<sup>st</sup> Century Review Milestones** (optional):

Day 74 Letter Date: 8/16/10

Review Completion Goal Date:

o primary (2/27/11)- 5 wks before action;

o secondary (3/6/11)- 4 wks before action

Labeling/PMC/PMR discussion- 3/11/11 (can be earlier; 3 wks before action)

PDUFA Goal Date: 4/3/11

**Comments:**

### REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

### ACTIONS ITEMS

<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day</li> </ul>

	filing letter; For NDAs/NDA supplements: see CST for choices) <ul style="list-style-type: none"><li>• notify DMPQ (so facility inspections can be scheduled earlier)</li></ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201152

-----  
ORIG-1

-----  
BOEHRINGER  
INGELHEIM  
PHARMACEUTICA  
LS INC

-----  
Nevirapine Extended Release  
Tablets

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMALIA C HIMAYA  
07/16/2010