

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203137Orig1s000

OTHER REVIEW(S)

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

Final Label and Labeling Memo

Date: October 24, 2013

Reviewer: Tingting Gao, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Vizamyl (Flutemetamol F18) Injection
150 MBq per mL (4.05 mCi per mL)

Application Type/Number: NDA 203137

Applicant/sponsor: GE Healthcare

OSE RCM #: 2013-2355

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised Vizamyl vial and shield label for Vizamyl, NDA 203137, submitted by the Applicant on October 11, 2013 (Appendices A through D). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2012-2632 dated March 25, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling submitted by the Applicant on October 11, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2012-2632 dated March 25, 2013.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. DMEPA concludes that the revised labels and labeling are acceptable.

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 OSE Regulatory Project Manager, Teena Thomas, at 301-796-0549.

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

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/s/

TINGTING N GAO
10/24/2013

YELENA L MASLOV
10/24/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: October 11, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Medical Imaging Products (DMIP)

Sponsor: GE Healthcare

NDA/Drug: 203137/Vizamyl (flutemetamol F 18) Injection

Route of Administration: Intravenous

Indications: A radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.

Consult Request: Please review proposed labeling changes and provide comment on the acceptability of the proposed changes to section 8.1.

INTRODUCTION

On October 26, 2012, GE Healthcare submitted a New Drug Application (NDA) for Vizamyl (flutemetamol F 18) injection. Vizamyl is a radioactive diagnostic agent (radiopharmaceutical) with a proposed indication for use with Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.

On August 5, 2013, the Agency sent revised labeling to the applicant. On August 9, 2013, the applicant submitted revised labeling to the Agency that included revisions under the Pregnancy section. The DMIP consulted the PMHS-MHT on August 22, 2013 requesting review and comment regarding the acceptability of the applicant proposed labeling revisions under Pregnancy, section 8.1 of labeling. DMIP requested feedback within two weeks of the consult date.

BACKGROUND

Reproductive developmental toxicology studies were not performed for flutemetamol F 18 injection and there are no animal reproductive toxicology data for Vizamyl. On July 8, 2009, the applicant requested a waiver for reproductive toxicology studies under 21 CFR 312.10, as flutemetamol F 18 injection is intended for single or infrequent use with significant time intervals between treatments. A waiver was granted by the Agency on September 13, 2010. There are no available human data evaluating use of Flutemetamol F18 Injection during pregnancy.

Another diagnostic radiopharmaceutical, Amyvid (florbetapir F 18), is currently the only approved product for use with PET imaging for evaluation of brain β amyloid neuritic plaque density. Amyvid was approved on April 6, 2012. The PMHS-MHT was consulted to review Amyvid labeling, and labeling recommendations were provided in a review dated February 28, 2012. Like Vizamyl, reproductive toxicology studies were waived for Amyvid and there are no animal reproductive toxicology data or available human pregnancy data for Amyvid.

REVIEW OF SUBMITTED MATERIALS

The PMHS-MHT reviewed the applicant's proposed Vizamyl labeling submitted August 9, 2013. PMHS-MHT preliminary labeling recommendations were provided to DMIP via email on August 27, 2013. A summary of PMHS-MHT labeling recommendations appear immediately following the Discussions section of this review.

Applicant Proposed Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: (b) (4)

It is (b) (4) not known whether Vizamyl can cause fetal harm when administered to a pregnant woman or if it can affect reproduction capacity. All radiopharmaceuticals, including Vizamyl, have the potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the magnitude of the radiopharmaceutical dose. Vizamyl should be given to a pregnant woman only if clearly needed. Assess pregnancy status before administering Vizamyl to a female of reproductive capacity.

DISCUSSION

The PMHS-MHT acknowledges that the use of Vizamyl in pregnant women will be most likely rare, as the diagnostic indication for Vizamyl (imaging of β -amyloid plaques, a pathologic finding in Alzheimer's disease) is rare among females of reproductive potential. However, should use of Vizamyl become medically necessary during pregnancy, there is potential for embryo-fetal harm, depending on gestational age and the dose of radiation received.¹ Therefore, appropriate use information should be available for pregnant female patients and females of reproductive potential to reasonably minimize exposure of the patient and subsequent fetal exposure.²

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. Generally, PMHS-MHT structures Pregnancy label information in the spirit of the Proposed Rule, while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling would provide a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow would provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. However, there are no available animal or human reproductive data to describe in labeling as noted above. Therefore, labeling was revised according to current regulations and to align with current PMHS-MHT recommendations for appropriate regulatory language. PMHS-MHT recommendations also align with current Amyvid labeling content.

PMHS-MHT Labeling Recommendations (labeling excerpts)

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Nursing Mothers: If Vizamyl is administered to a nursing woman, interrupt nursing for 24 hours (8.3).

¹ Website:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/Pregnancy.aspx. American College of Radiology, 2008.

² Website:

http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/Pregnancy.aspx. American College of Radiology, 2008.

Reviewer Note: PMHS-MHT was not consulted regarding nursing mothers labeling language. However, PMHS-MHT recommends adding the above bulleted statement regarding nursing mothers to the Highlights of Prescribing Information, under Use in Specific Populations to align with language in the Nursing Mothers Section 8.3. PMHS-MHT provided the same recommendation previously in a review of Amyvid labeling dated February 28, 2012.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

It is not known whether Vizamyl can cause fetal harm when administered to a pregnant woman or if it can affect reproduction capacity. Animal reproduction studies have not been conducted with Vizamyl. All radiopharmaceuticals, including Vizamyl, have the potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the magnitude of the radiopharmaceutical dose. Vizamyl should be given to a pregnant woman only if clearly needed. Assess pregnancy status before administering Vizamyl to a female of reproductive potential.

*Reviewer Note: The last sentence of paragraph was revised to read “Assess pregnancy status before administering Vizamyl to a **female of reproductive potential**.” The term “female of reproductive potential” is recommended by PMHS-MHT to describe female patients who are able to become pregnant and is the language currently used across other labeling and REMS products.*

CONCLUSIONS

The DMIP consulted the PMHS-MHT to provide review and comment regarding the acceptability of the applicant proposed labeling revisions to the Pregnancy section (8.1) of labeling. PMHS-MHT concurs with the content of the applicant’s labeling, however, recommends the minor revisions as stated in the labeling excerpts above under PMHS-MHT Labeling Recommendations. These labeling recommendations are unchanged from those outlined in the August 27, 2013 email recommendations to DMIP.

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/s/

TAMMIE B BRENT HOWARD
10/11/2013

JEANINE A BEST
10/11/2013

LYNNE P YAO
10/12/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	VIZAMYL (flutemetamol F 18 injection), for intravenous use
Applicant	GE Healthcare
Application/Supplement Number	NDA 203137
Type of Application	Original Submission (NME)
Indication(s)	For Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.
Established Pharmacologic Class ¹	radioactive diagnostic agent
Office/Division	ODE IV/DMIP
Division Project Manager	Sharon Thomas
Date FDA Received Application	October 26, 2012
Goal Date	October 26, 2013
Date PI Received by SEALD	September 11, 2013
SEALD Review Date	September 13, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: Top margin of HL is greater than 1/2 inch.

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: Statement for "most commonly reported adverse reactions are" must reference (6) at the end of this statement. It's missing. The reference "(6)" that is at the end of the bolded adverse reaction reporting statement is incorrect; delete.

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**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).**”

Comment: *The name of drug product (Vizamyl) is not in upper case, and should be (VIZAMYL).*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

N/A

Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subsection heading 6.1 in TOC is "Clinical Trials Experience" (which is correct); however, subsection heading 6.1 in the FPI is "Clinical Trial Experience." The "s" is missing from the word "Trials."*

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information

Comment:

- NO** 33. All subsection headings must be indented, not bolded, and in title case.
Comment: Subsection heading 5.2, "other" should be "Other". Use upper case "O".

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) 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.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“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.”

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”

Comment:

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “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)”

Comment:

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/s/

JEANNE M DELASKO
09/13/2013

LAURIE B BURKE
09/15/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: May 31, 2013
To: Sharon Thomas,
Regulatory Project Manager
Division of Medical Imaging Products (DMIP)
From: Adora Ndu,
Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)
Subject: NDA 203137
OPDP comments for Vizamyl (Flutemetamol F-18 Injection)
Package Insert (PI)

On December 4, 2012, OPDP received a consult request from DMIP to review the proposed PI for Vizamyl (Flutemetamol F-18 Injection).

OPDP has reviewed the proposed labeling using the following versions of the proposed labels received from DMIP on May 20, 2013:

- LY-5-7-13Vizamyl_DRAFT.docx

After review of the proposed labeling, OPDP offers the following comments. Please note that comments are included within the proposed PI.

If you have any questions regarding the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

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

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/s/

ADORA NDU
05/31/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 3, 2013

TO: Sharon Thomas, Regulatory Project Manager
Phillip Davis, M.D., Clinical Reviewer
Lucie Yang, M.D., Ph.D., Clinical Team Leader
Division of Medical Imaging Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader
Susan Thompson, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 203-137

APPLICANT: GE HealthCare, Inc.

DRUG: Vizamy[®] (flutemetamol)

NME: Yes

INDICATION: Use in positron emission tomography to evaluate Alzheimer's disease

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: December 10, 2012

INSPECTION SUMMARY GOAL DATE: July 26, 2013

DMIP ACTION GOAL DATE: October 25, 2013

PDUFA DUE DATE: October 26, 2013

I. BACKGROUND

Alzheimer's disease (**AD**) is the most common cause of dementia in the elderly, affecting over 4 million people in the United States (**US**) alone. Mild cognitive impairment (**MCI**), an intermediate stage between dementia and the expected cognitive decline of normal aging, appears to be a risk factor for AD. Although the etiology of AD remains unknown, the amyloid-beta peptide fibrils (amyloid-beta) appear to be important to its pathogenesis. Accumulation of amyloid-beta is the hallmark of the disease and a key confirmatory histopathologic criterion at autopsy. Most AD cases occur sporadically, but rare familial mutations are known to be genetically inherited (autosomal dominant). Transgenic mice with one or more of the mutant human genes develop amyloid plaques and show behavioral deficits that parallel those in AD patients. Experimental therapies that reduce the amyloid-beta load (decrease production and/or increase clearance) have been successful in reversing the behavioral deficits in affected mice. Some of these novel therapies are now entering human trial. Clinical diagnosis of AD is often inaccurate, and is often proven incorrect at autopsy.

Flutemetamol F 18 Injection (Vizamyl[®]) was developed by GE Healthcare under US IND 101866 as a diagnostic radiopharmaceutical for use with positron emission tomography (**PET**) to visually detect amyloid-beta (neuritic plaques) in the brain of patients being evaluated for (b) (4) AD. Vizamyl[®] PET is to be used as an adjunct to other diagnostic evaluations: a normal Vizamyl[®] PET scan (sparse or no neuritic plaques) rules out AD, but an abnormal scan (moderate to frequent neuritic plaques) does not rule out normal cognition or other (non-AD) cognitive disorders. The clinical utility of Vizamyl[®] PET has not been established for predicting dementia (or other neurological conditions) or for monitoring therapeutic response. The active component of Vizamyl[®] is a fluorinated derivative of Pittsburgh Compound B, a well-known PET amyloid imaging agent with reversible affinity for amyloid. The short radioactive half-life of fluorine-18 makes it necessary to manufacture, purify, assay, and deliver Vizamyl[®] to the end user within a single day.

Vizamyl[®] is a new molecular entity (**NME**) similar to Amyvid[®] (florbetapir F 18), a product in the same pharmacologic class and currently approved in the US for the same clinical indication. To support CDER's review of the current NDA, the following three pivotal Vizamyl[®] studies have been identified for good clinical practice (GCP) inspection.

Study GE-067-007

A Principal Open-Label Study to Compare the Brain Uptake of [18F] Flutemetamol with Brain Fibrillar Amyloid β Levels Determined Post-mortem

This open-label PET study was conducted over 17 months, from June 2010 to November 2011, in 180 subjects at 19 clinical study sites (15 in US, 4 in United Kingdom). Images from 176 subjects were evaluable for PET efficacy. The primary study objective was to determine the sensitivity of Vizamyl[®] PET without using reference anatomic imaging in detecting brain amyloid-beta. Independent (off-site) image interpretation was coordinated by Grove Center located at Amersham, United Kingdom (**UK**), an imaging division of the sponsor and not a contract research organization (**CRO**).

Subject Selection

- Inclusion Criteria
 - Age \geq 55 years, terminal illness (life expectancy \leq one year), reliable caregiver
 - Women: surgically sterile, postmenopausal ($>$ 2 years), or negative pregnancy test
- Exclusion Criteria
 - Any structural brain abnormality or lesion which may interfere with PET image interpretation
 - Hypersensitivity to Vizamyl[®] or to any of its excipients
 - Pregnancy or lactation; receipt of any investigational agent within 30 days

Study Procedures

- Blinding: Study personnel were not blinded to Vizamy[®] identity in this open-label study; however, all personnel were blinded to all other clinical data. Those involved in image processing and analysis were blinded to histopathology data, and conversely, those involved in histopathology were blinded to imaging data. Subjects were blinded to imaging results.
- Study visits: (1) screening visit within 35 days of Vizamy[®] injection, (second visit if anatomic imaging and clinical assessment were not completed in one visit), and (2) PET imaging visit
- Vizamy[®] administration and brain imaging: (1) anatomic imaging, typically computed tomography (CT); (2) open-label Vizamy[®] intravenous (IV) injection, typically within 40 seconds, 185-370 MBq (5-10 mCi); and (3) PET imaging over 30 minutes, 90 minutes after Vizamy[®] injection
- PET image interpretation: Images were read by five independent readers blinded to the standard of truth (SOT) and all clinical data.
 - Without anatomic images: PET images (grouped into image sets) were read as either normal or abnormal (negative or positive for amyloid-beta). Each image set was completed before proceeding with the read of the images in the next image set.
 - With anatomic images: After completing all PET image sets, the images/sets were re-randomized and re-presented with corresponding anatomic images. Read results were classified as either normal or abnormal (negative or positive for amyloid-beta).

SOT Determination

Subjects were followed until death or study termination. The brains of subjects who died during the study were examined histopathologically for neuritic plaque density by blinded personnel.

- Normal versus abnormal brain for neuritic plaques was determined using a pre-defined threshold score of 1.5 using the modified Consortium to Establish a Registry for AD (CERAD) scale.
- Specimens were taken from eight cortical regions (left hemisphere): precuneus, mid-frontal, superior temporal, middle temporal, inferior parietal, anterior cingulate, posterior cingulate, and primary visual
- Total of 48 slides per subject (8 x 2 x 3 = 48): eight brain regions per subject, two tissue blocks (anterior and posterior) per region, three microscopic slides per block; slides prepared with standard and Bielschowsky special stains
- Five microscopic field scores per slide: each field scored from 0 to 3 based on the number of neuritic plaques per 100-fold magnification field using the CERAD scale: 0 (0), 1 (1-5), 2 (6-19) or 3 (≥ 20)
- Slide score = mean of 5 field scores, region score = mean of 6 slide scores, normal region = region score < 1.5, abnormal region = region score ≥ 1.5 , abnormal brain = at least one region abnormal

Major Endpoints and Analyses

- Primary Efficacy: PET image interpretation as either normal or abnormal, without anatomic brain images, by five independent blinded readers trained in reading PET amyloid-beta images
 - Sensitivity of Vizamy[®] PET *without* anatomic reference imaging in detecting amyloid-beta, as determined using histopathology as SOT
 - Sensitivity of Vizamy[®] PET was deemed clinically useful if the lower bound of two-sided 95% confidence interval (CI) exceeded 70% for at least three readers.
- Secondary Efficacy: Performance characteristics of Vizamy[®] PET in visually detecting amyloid-beta as determined for each of five readers using histopathology as SOT

- Sensitivity *with* anatomic reference imaging
- Specificity *with* and *without* anatomic reference imaging
- Global and region-specific standard uptake value ratio (**SUVR**) for Vizamyl[®]

Note: SUVR is a quantitative measure of Vizamyl[®] uptake normalized for uptake in a reference region where amyloid-beta is expected to be absent (cerebellar cortex or pons)

- Safety: Clinical follow up for 24 hours (> 5 Vizamyl[®] elimination half-lives)
 - Adverse event (**AE**) monitoring, physical and neurological examinations, vital signs
 - Electrocardiogram (**ECG**), clinical laboratory testing (chemistry, hematology, coagulation)

Major Findings

- Of the 180 subjects enrolled (dosed, safety population), 176 were evaluable for PET efficacy. Autopsy and histopathologic evaluation in 68 subjects provided SOT data.
- Vizamyl[®] PET appeared to be sufficiently sensitive and specific to be clinically useful without anatomic brain imaging in detecting brain amyloid-beta. Availability of reference anatomic imaging (CT) did not significantly increase the performance characteristics of Vizamyl[®] PET.
 - Mean sensitivity *without* CT: 89%, 95% CI of 67-99% (lower bound > 70% in 4 readers)
 - Mean sensitivity *with* CT: 93%, 95% CI of 77-100% (lower bound > 70% in all 5 readers)
 - Mean specificity: 79% without CT and 83% with CT
 - Results with and without CT not statistically significant/different
- A single injection of Vizamyl[®] at 185-370 MBq (5-10 mCi) appeared to be well tolerated in this population of terminally ill subjects.

Study GE-067-015

A Single-Arm Open-Label Multi-Center Study to Determine the Specificity of Flutemetamol F 18 Injection for Excluding the Presence of Brain Amyloid in Healthy Young Adult Subjects Aged 18 to 40

This was an open-label PET study conducted over three months (December 2010 to March 2011) in 181 subjects at ten clinical sites: 6 in US, 2 in UK, and one each in Finland and Belgium. The primary study objective was to determine the specificity of Vizamyl[®] PET for amyloid-beta in healthy subjects of age 18 to 40 years. The images from healthy subjects in this study were mixed (random and blinded order) with those from subjects with MCI in a previous Study GE-067-005. The abnormal images from the MCI study made it possible to objectively evaluate the images from this study, without knowing that they are normal. In determining the specificity of Vizamyl[®] PET, however, only the images from healthy subjects were used. The enrollment criterion of health served as the SOT; Vizamyl[®] PET images from healthy subjects were assumed to be negative for amyloid-beta. Images were read by 5 independent blinded (to health versus MCI) readers at Grove Center.

Subject Selection

- Inclusion Criteria
 - Healthy, age between 18 and 40 years, no history of cognitive impairment
 - Mini-Mental State Examination (**MMSE**) score \geq 28
 - Normal magnetic resonance imaging (**MRI**) of the brain at screening
 - At least 6 years of education or good work history
 - Women: surgically sterile, postmenopausal (> 3 years), or negative pregnancy test
- Exclusion Criteria
 - Family history of AD (birth parents and siblings); history of head injury with loss of consciousness
 - Any clinically significant medical, psychiatric, or neurological condition

- Any abnormality that might indicate brain pathology
- Contraindication for MRI (including claustrophobia, pacemaker, and metallic implants)
- Exposure to medical ionizing radiation in the last 12 months, except planar X-ray or head CT
- Monitoring for occupational radiation; history of alcohol and/or drug abuse within 2 years
- Pregnancy or lactation; receipt of any investigational agent within 30 days
- History of HIV or hepatitis infection; hypersensitivity to Vizamyl[®] or to any of its excipients

Study Procedures

- Study visits: (1) screening visit within 45 days of Vizamyl[®] administration, (2) second screening visit if anatomic imaging (magnetic resonance imaging, MRI) and/or clinical assessment could not be completed in one screening visit, and (3) PET imaging visit
- Vizamyl[®] administration and PET: open-label Vizamyl[®] IV injection, typically within 40 seconds (185-370 MBq, 5-10 mCi, or 6 mSv), followed in 90 minutes by PET imaging over 30 minutes
- Vizamyl[®] PET images from GE-067-015 and the previous GE-067-005 studies were mixed (random blinded order) and read by 5 independent readers trained in PET brain amyloid imaging.
- SOT: The subjects enrolled in this study, healthy young adults of age 18 to 40 years, were presumed to be amyloid negative. This assumption constituted the SOT for this study.

Major Endpoints and Analyses

- Primary Efficacy: Each reader categorized the Vizamyl[®] PET images from both studies (GE-067-015 and GE-067-005) as either normal or abnormal for amyloid-beta.
 - Specificity of Vizamyl[®] PET was calculated using only the read results for the images from the current study, using the enrollment criterion of health as the SOT (all subjects presumed to be negative for amyloid-beta on Vizamyl[®] PET).
 - Vizamyl[®] PET was deemed sufficiently specific to be clinically useful if the lower bound of the 95% CI exceeded 80% in at least three readers.
- Secondary Efficacy: Composite average SUVR for 5 brain areas (frontal, anterior cingulate, parietal, lateral-temporal, and posterior cingulate/precuneus)
- Safety: Clinical monitoring during Vizamyl[®] injection and PET and by phone at 24 hours
 - AE monitoring, physical and neurological examinations, vital signs
 - ECG, clinical laboratory testing (chemistry, hematology, coagulation)
 - Subjects instructed to report serious AEs (SAE) occurring within 30 days

Major Findings

- Vizamyl[®] PET appeared to be sufficiently specific to be clinically useful. Mean specificity was 93%, with 95% CI of 61-100% (lower bound > 95% in 4 readers). For 4 readers, inter-reader and intra-reader concordance was 99-100% (for fifth reader, 68% and 75%, respectively).
- Twenty-seven (15%) subjects reported transient and mild AEs, most commonly flushing (6%), chest discomfort (4%), and nausea (3%). There were no SAEs or deaths. There were no significant changes in physical and neurological examination, vital signs, clinical laboratory results, and ECG. Vizamyl[®] and PET appeared to be well tolerated in healthy subjects of 18 to 40 years of age.

Study GE-067-021

A study to evaluate the effectiveness of an electronic training program for orienting and interpreting [18F] flutemetamol Positron Emission Tomography images

This Vizamy[®] PET training study "enrolled" 5 technologist and 5 physician trainees; no subjects were enrolled and no study medication was administered. The primary study objective was to evaluate the effectiveness of an electronic program as a self-training tool for orientating and reading Vizamy[®] PET images. Five nuclear medicine technologists (NMT) and 5 blinded physician readers (nuclear medicine physicians and/or radiologists) were trained using the DVD-based program.

To validate the program for its training effectiveness, images from prior Vizamy[®] PET studies were evaluated by program-trained NMTs and physician readers and their adequate diagnostic performance was shown by sensitivity and specificity each exceeding 70%. The study was conducted over one month (July-August 2012) at a single CRO site, (b) (4)

Image and Candidate Selection

- Vizamy[®] PET images: 276 unique images were selected from prior Vizamy[®] PET studies to represent the full spectrum of cognition (normal to dementia including AD). To assess inter-reader and intra-reader agreement, 29 of the 276 images (10%) were selected at random, duplicated, and randomly inserted into the original pool for a total of 305 images for blinded reading.
- Candidate NMTs: Practicing in US and certified by American Registry of Radiologic Technologists or Nuclear Medicine Technology Certification Board and experienced in acquisition, processing, and orientation of nuclear medicine images of the brain (excluded if experienced in amyloid imaging)
- Candidate Readers: Practicing in US and board-certified in nuclear medicine or radiology with training and clinical experience in nuclear medicine, with extensive experience reading nuclear medicine images in a clinical setting (excluded for any prior experience in reading amyloid images)

Study Procedures

- *Training of Candidate NMTs and Readers:* The selected candidates (NMT and physician readers) were asked to complete the DVD-based electronic training program.
 - The training program was designed for self-training in assessing Vizamy[®] PET images for proper orientation and to correct the orientation if necessary (NMTs and readers), and to correctly and reproducibly classify the images as either normal or abnormal (readers only). The training program included NMT and reader tests.
 - Reader Test: Successful reader training was defined as $\geq 90\%$ agreement of test image reads between the candidate reader and an expert Vizamy[®] PET imaging consultant.
- *Blinded Image Reads:* None of the images in the training program were included in the 305 study images read by the first 5 candidate readers passing the reader test (described above).
 - Each of the first 5 NMT candidates passing the NMT test (not described above) were asked to assess (and re-orient as necessary) one fifth of the 305 images (61 images) selected at random. The NMTs oriented the images into standard views and the oriented images were randomized for blinded reading. Two NMTs remained on call for reader assistance.
 - All 305 study images were read by each of the 5 readers. The images were read as either *normal* or *abnormal*, and the result was recorded on a case report form (CRF) along with self-rating of confidence. The readers were not permitted to exclude any image.

Major Endpoints and Analyses

- Seven analysis populations were defined, of which Analysis Population 1 consisted of 135 subjects with an SOT of any type: 68 from Study GE-067-007; 36 from Studies GE-067-009, GE-067-010, and GE-067-011; and 31 from Study GE067-015. This Analysis Population 1 was used for the primary and secondary analyses (without and with anatomic images, respectively) of Vizamy[®] PET

validity (sensitivity and specificity). For the 29 images duplicated for reader agreement determination, the first image interpretation was used for efficacy analysis.

- Vizamy1[®] PET was deemed valid (clinically useful sensitivity and specificity) if the lower bounds of the two-sided 95% CIs for sensitivity and specificity were each >70% in at least three readers.

Major Findings

- The DVD-based electronic program appeared to be effective in training previously inexperienced personnel to interpret amyloid images with high sensitivity, specificity, predictive value (positive and negative), and reader reproducibility (inter-reader and intra-reader agreement).
- The lower bounds of the two-sided 95% CIs for both sensitivity and specificity exceeded 70% for three readers. The availability of CT images did not significantly affect the results. The high negative predictive values indicated that a negative Vizamy1[®] PET image rules out AD. Subset analysis showed no significant difference in effectiveness between electronic versus in-person training. Diagnostic specificity tended to be higher (non-significant) with electronic self-training.

II. INSPECTIONS

Five sites were inspected as shown below: (1) sponsor, GE HealthCare; (2) sponsor's site for blinded image evaluations (BIE), Grove Center; (3) histopathology CRO, (b) (4); (4) CRO for Study GE-067-021, (b) (4); and (5) data management CRO, (b) (4).

	Inspected Entity (Role)	Studies and Subjects	Inspection Dates	Outcome
1	GE HealthCare (sponsor)	GE-067-007: 176 subjects GE-067-015: 181 subjects GE-067-021: 276 subjects	(b) (4)	VAI
2	Grove Center (sponsor BIE site)	GE-067-007: 176 subjects GE-067-015: 181 subjects	(b) (4)	NAI
3	(b) (4) (histopathology CRO)	GE-067-007: 68 subjects	(b) (4)	NAI
4	(b) (4) (training study CRO)	GE-067-021: 276 subjects	(b) (4)	NAI
5	(b) (4) (data management CRO)	GE-067-007: 176 subjects GE-067-015: 181 subjects	(b) (4)	NAI

NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations); OAI = official action indicated (serious GCP deviations and/or data unreliable)

1. GE HealthCare, Inc. (Princeton, NJ)

a. What was inspected:

- Compliance with good clinical practice (GCP) regulations, study protocols, and standard operating procedures (SOPs) as applicable to clinical site monitoring, electronic data controls, and test article accountability
- Verification of data for image randomization, PET image evaluations, histopathology SOT, and reader confidence

b. General observations:

A Form FDA 483 was issued for inadequate study monitoring (or follow up corrective action) of Study GE-067-007, as shown below for all (three) sites audited for this study. Monitoring and oversight of the other pivotal studies (Studies GE-067-015 and GE-067-021) appeared adequate.

- Study GE-067-007, Site 115, Gamez (Miami Springs, FL): 34 subjects
 - Subject enrollment exceeded the IRB-approved limit (25 subjects) by 9 subjects, without IRB approval for the additional 9 subjects.
 - Documentation of IRB approval was not available. Further, the IRB form (*Confirmation of Closure and Conclusion of IRB Oversight*) was not sent to the IRB. The study monitor reported this deficiency but the sponsor failed to follow up with corrective action.
- Study GE-067-007, Site 122, Singh (Las Vegas, NV): 30 subjects
 - Clinical investigator Limuaco (performed at least one autopsy) and [REDACTED] (b)(4). (ApoE genotyping) were not listed on Form FDA 1572.
 - Financial disclosures were not obtained for three of eight clinical investigators (Limuaco, Jones, and Taylor) who had signed the *Delegation Signature Log*.
 - In 6 of 10 subject records reviewed, ECGs were not documented as having been performed within 4 hours of the PET scan.
- Study GE-067-007, Site 124, Curtis (Orlando, FL): 35 subjects
 - Clinical investigator Pearl (performed 5 autopsies) was not listed on Form FDA 1572.
 - Financial disclosures were not obtained for two of seven clinical investigators (Pearl and Verna) who had signed the *Delegation Signature Log*. For clinical investigator Pearl, the deficiency was noted by the study monitor and reported to the sponsor, but the sponsor's one-time reminder was inadequate to achieve compliance.
 - Enrollment of subjects over the IRB-approved limit preceded the date of IRB approval for increased subject enrollment (by 16 days).
 - The final IRB form was not sent to the IRB. The study monitor reported this deficiency but the sponsor failed to follow up with corrective action.

Other than as noted above, no deficiencies were observed. The audited study data were verifiable. Electronic data controls and test article accountability appeared to be adequate.

c. Assessment of data integrity:

The observed deficiencies do not appear significant and are unlikely to have importantly affected the study outcomes. Efficacy data were not obtained at the clinical study sites and no significant AEs were observed, including no cardiac AEs. The study data appear reliable as reported in the NDA.

2. The Grove Center (Buckinghamshire, UK)

- a. What was inspected:
 - Audit of Studies GE-067-007 and GE-067-015
 - Compliance with applicable GCP regulations, study protocols, imaging charters, and SOPs
 - Integrity of the study blind in interpreting PET images
 - Images reviewed: 15 for each study
 - Data verification (CRF and NDA data): 35 subjects for each study
- b. General observations:
 - No significant deficiencies were observed and a Form FDA 483 was not issued.
 - There was no evidence of image unblinding or biased image interpretation.
 - The primary efficacy data in the NDA were verifiable against the corresponding CRFs.
 - Study monitoring and drug accountability records appeared adequate.

Reviewer Comments

The BIE Workstation: BIE of PET images were performed at this satellite sponsor site. The BIE workstation consisted of a laptop computer with built-in software (Xeleris[®]) which had been FDA-cleared for retrieving and archiving electronic images from a central database. On scheduled days of image interpretation, images were down-loaded using Xeleris[®] from a central server (Medstamp[®]) in Oslo, Norway and made available on five laptops for the five readers.

To help maintain the study blind, image down-loading was performed as a study function distinctly separate from image interpretation; image down-loading and image interpretation were performed by different study personnel in two separate buildings. Image readers entered their interpretation on paper CRFs. The down-loaded electronic images were not archived for subsequent review or audit.

At inspection, how the images were read at the BIE workstation was recreated and demonstrated. For each study (GE-067-007 and GE-067-015), an examination of 15 randomly selected images appeared to be consistent with the corresponding CRF data, and no discrepancies were noted between the CRFs and the NDA data listing.

Product Dilution: Early in Study GE-067-007, at all 4 UK imaging Sites 104, 105, 909, and 911, the study medication had been inappropriately diluted (approximately 5-fold) during product preparation at 2 UK product preparation Sites 110 and 912. At least 7 subjects were given the diluted product (Subjects 1040001-1040004, 1050002-1050004).

The product was diluted with saline to reduce radiation exposure during product preparation. Using the same (originally intended) final volume of a diluted product, rather than using less undiluted product, allowed the reduced dose to be measured with adequate accuracy. This unauthorized dilution practice was corrected at discovery of the violation at study monitoring.

The sponsor retained the affected study data: image quality was deemed acceptable, and no adverse events were expected (none observed). This deficiency was verbally discussed and not cited on Form FDA 483 per inspector discretion. In the NDA, product dilution was not reported as a protocol violation for the affected sites and subjects.

- c. Assessment of data integrity:

For Study GE-067-007, the significance of product dilution is deferred to DMIP; it appears unlikely to have importantly affected the study outcome. For the two studies audited at this satellite sponsor site, (Studies GE-067-007 and GE-067-015), the study data appear reliable as reported in the NDA.

3. [REDACTED] (b) (4)

a. What was inspected:

- Audit of Study GE-067-007
- Compliance with applicable GCP regulations and contractual agreement with sponsor
- Adherence to the study protocol and applicable SOPs (including *Pathology Manual*)
- Integrity of the study blind in interpreting histopathology SOT
- Histopathology SOT data verification (CRF and NDA data) for all 68 subjects

b. General observations:

- No significant deficiencies were observed and a Form FDA 483 was not issued.
- There was no evidence of unblinding or biased histopathology interpretation.
- The primary efficacy data in the NDA were verifiable against the corresponding CRFs.
- Study monitoring by the sponsor (GE HealthCare) appeared adequate.

Reviewer Comments

Data Verification: [REDACTED] (b) (4) had contracted out histopathology evaluation to four specialists: tissue sampling and initial evaluation of conventional histopathology by two neuropathologists, followed by SOT determination by two (other) neuropathologists. The two SOT neuropathologists reviewed the microscopic slides together using a double-headed microscope, and consensus SOT results were recorded directly on CRFs without using source documents.

The original consult (Request for Inspections) notes 69 subjects for SOT histopathology evaluation. Subject 122-0022 (Sample 1026) died after a fall and was referred to the medical examiner. This subject was excluded from the study, and the final pathology analysis population consisted of 68 subjects.

For all 68 subjects, the corresponding NDA and CRF data matched, and the data appeared to be consistent with histopathology as demonstrated during inspection using a double-headed microscope. SUVR was determined only for the first 30 subjects. An Excel spreadsheet (without CRFs) was used to record SUVR data. For all 30 subjects, the NDA data were verifiable against the source data on the Excel spreadsheet.

Financial Disclosure: For the four neuropathologists, two were obtained late during study investigation, one was provided upon request during inspection, and one remained unavailable at close of inspection. [REDACTED] (b) (4) noted that the sponsor obtains financial disclosure.

c. Assessment of data integrity: The study data appear reliable as reported in the NDA.

4. [REDACTED] (b) (4)

a. What was inspected:

- Compliance with applicable GCP regulations, study protocols, SOPs, and contract with sponsor; and verification of data for Study GE-067-021
- Adherence to protocol-related documents specific to Study GE-067-021: *Independent Review Charter* and *Monitoring Plan*
- Robustness of database controls, including how easily data can be modified and if each modification is automatically documented for subsequent tracking, review, and audit

b. General observations:

- No significant deficiencies were noted and a Form FDA 483 was not issued. A total of 345 CRFs for 32 subjects were audited.

- 32 PET-only cases, 5 readers per case: 160 reader decisions
- 29 MR/CT cases, 5 readers per case: 145 reader decisions
- 3 PET-only re-read cases, 5 readers per case: 15 reader decisions
- 5 MR/CT re-read cases, 5 readers per case: 25 reader decisions

One isolated data error was found. For Subject GE-067-007-104-0002, the NDA data listing incorrectly indicates Reader 5 response as normal (abnormal on CRF). This isolated error was confirmed to be the sponsor's error, and the deficiency was not cited on Form FDA 483.

- No more than 50 image sets were read at a single sitting without a break. The sponsor trained (b)(4) on-site on reader monitoring. Regarding electronic training:
 - On Day 1, all radiologists were trained using an electronic training program at one session. The primary training objective was to gain competency in assessing the brain cortex (diagramed on CRF), in classifying the cortical regions as either normal or abnormal.
 - The readers were qualified for study participation per protocol criteria, including the criterion for reader qualification test. All readers passed the test on first attempt (two attempts permitted). Upon passing the test, the readers received further training on using the PET/MRI workstations and on properly completing the CRFs.
 - The actual electronic training program was not available at inspection and could not be audited; the program was returned to sponsor at study completion.

c. Assessment of data integrity:

As a single isolated deficiency, the NDA data error for Subject 1040002 in Study GE-067-007 appears unlikely to affect the study outcome. The data from this study site appear reliable.

5. (b)(4)

a. What was inspected:

- Compliance with GCP regulations, study protocols, SOPs, and contract with sponsor
- Verification of PET image evaluation data for Studies GE-067-007 and GE-067-015
- Robustness of electronic controls over database interface, compatibility, and audit

b. General observations:

No deficiencies were noted and a Form FDA 483 was not issued. No discrepancies were noted between audited NDA data and source study records.

- (b)(4) performed data management and statistical programming for GE Healthcare, the sponsor of Studies GE-067-007 and GE-067-015. In managing study data, (b)(4) used ePower (electronic database) to view the image interpretation data on scanned images of the CRFs.
- Study GE-067-007: PET and corresponding histopathology SOT data were audited for 25 subjects at 6 clinical study sites, including 4 sites with the largest subject enrollment. CRFs were reviewed (using ePower) for three of five blinded readers for each subject. SUVR data were reviewed for five subjects at Site 104.
- Study GE-067-015: PET data were reviewed for 16 subjects by two blinded readers at (all) 10 clinical study sites.

c. Assessment of data integrity:

All audited efficacy data were verifiable. The data managed by (b)(4) for Studies GE-067-007 and GE-067-015 appear to be consistent with the data reported in the NDA.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

GE HealthCare has submitted an original NDA for flutemetamol (Vizamyl[®]), a diagnostic radiopharmaceutical NME for use with PET to evaluate AD. In support of the NDA review, 3 pivotal studies were audited at 5 sites, as summarized below.

Summary of Audited Pivotal Studies

- Study GE-067-007
 - Open-label brain autopsy study to correlate Vizamyl[®] uptake with beta-amyloid
 - Conducted over 17 months (June 2010 - November 2011)
 - 180 subjects at 19 centers (15 US, 4 UK), BIE for 176 subjects at Grove Center
 - Histopathologic SOT data from 68 subjects by (b) (4)
 - Sensitivity (~90%) and specificity (~80%) without adjunctive CT imaging
- Study GE-067-015
 - Open-label healthy volunteer study to evaluate Vizamyl[®] PET for ruling out beta-amyloid
 - Conducted over 3 months (December 2010 - March 2011), enrollment criterion of health as SOT
 - 181 subjects at 10 centers (6 US, 2 UK, 1 Finland, 1 Belgium), BIE at Grove Center
 - Specificity (~90%) inter-reader and intra-reader concordance nearly 100%
 - 27 subjects (15%) reported transient and mild AEs (flushing, chest discomfort, nausea)
- Study GE-067-021
 - Evaluation of effectiveness, electronic program for self-training, interpretation of Vizamyl[®] PET
 - Conducted over one month (July-August 2012) by (b) (4)
 - Self-training of 5 technologists and 5 physician trainees; no subjects and no study medication
 - Comparison of new trainee results against previous results as SOT
 - Sensitivity and specificity each > 70% with high intra-reader and inter-reader agreement

Summary of Inspection Outcomes

- GE HealthCare: Sponsor
 - VAI, audit of Studies GE-067-007, GE-067-0015, and GE-067-0021
 - Observed deficiency: Inadequate oversight of Study GE-067-007

Three clinical study sites were noted to have had excessive subject enrollment, inadequate FDA and IRB reporting, inadequate financial disclosures, and inadequate documentation about ECG.

- Grove Center: Sponsor's BIE center
 - NAI, audit of Studies GE-067-007 and GE-067-0015
 - Observed deficiency: Unauthorized product dilution at all UK sites early in Study GE-067-007

The data affected by unauthorized product dilution was retained in the NDA (deemed by the sponsor to have no effect on safety or efficacy). Product dilution was also not reported in the NDA as a protocol violation. Neither deficiency (product dilution and not reporting it as a protocol violation) was cited on Form FDA 483 (inspector discretion). The significance of product dilution is deferred to DMIP; it appears unlikely to have importantly affected the study outcome.

- (b) (4): Histopathology CRO
 - NAI, audit of Study GE-067-007
 - Observed deficiency: Inadequate financial disclosures

Financial disclosures for (all) four neuropathologists were inadequate (either late or absent). This deficiency was not cited (inspector discretion).

- (b) (4): CRO that conducted Study GE-067-021, image read training study
 - NAI, audit of Study GE-067-021
 - Observed deficiency: Isolated discrepancy between NDA and CRF data

The discrepancy was determined to be the sponsor's error (not cited on Form FDA 483). The actual electronic training program was not available at inspection (no demonstration and audit).

- (b) (4): Data management CRO
 - NAI, audit of Studies GE-067-007 and GE-067-0015
 - Observed deficiency: None

In brief, minor isolated deficiencies were observed at four of the five sites inspected, including three sites with an NAI final inspection outcome. For Study GE-067-007, the significance of product dilution is deferred to the review division. None of the observed deficiencies appear significant, and all audited study data appear reliable as reported in the NDA. The deficiencies are nonetheless summarized above to facilitate the on-going NDA review (should they prove significant).

{See appended electronic signature page}

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

Label, Labeling and Packaging Review

Date: March 25, 2013

Reviewer: Kevin Wright, PharmD
Division of Medication Error and Prevention Analysis

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Drug Name and Strength: Vizamyl (Flutemetamol F18) Injection
150 MBq per mL (4.05 mCi per mL)

Application Type/Number: NDA 203137

Applicant/sponsor: GE Healthcare

OSE RCM #: 2012-2632

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, shield and insert labeling for Vizamyl NDA 203137 for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the October 26, 2012 submission.

- Intended pronunciation: viz-amil
- Active Ingredient: Flutemetamol F18
- Indication of Use: indicated for use with positron emission tomography (PET) imaging to detect fibrillar amyloid in the brain
- Route of Administration: Intravenous
- Dosage Form: Solution for Injection
- Strength: 150 MBq per mL (4.05 mCi per mL)
- Dose and Frequency: 185 MBq (5 mCi) for one dose
- How Supplied: 10 mL and 30 mL multi-dose glass vials
- Storage: store at 2° to 30° C (36° to 86° F); (b) (4)
(b) (4)
- Container and Closure Systems: 10 mL and 30 mL glass vials with aluminum flip off seal

2 METHODS AND MATERIALS REVIEWED

We reviewed the labels and labeling submitted by the applicant and compared them to other imaging agent such as Amymid that is currently marketed. We also searched the FDA Adverse Event System (FAERS) database for errors occurring with Avymid since these are similar products and any errors occurring Avymid due to the labels and labeling may be relevant to this review.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) a database using the strategy listed in Table 1. The FAERS database search identified zero cases.

Table 1: FAERS Search Strategy	
Date	March 12, 2012
Drug Names	Amyvid (product name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues (NEC) HLT

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 26, 2012(Appendices A and C)
- Shield Labeling submitted October 26, 2012 (Appendices B and D)
- Insert Labeling submitted October 26, 2012 (no image)

3 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Comments to the Division
 1. Insert Labeling
 - a. General Comment
 - Revise the proposed proprietary name throughout the labels and labeling to title case (i.e. Vizamyl).
- B. Comments to the Applicant
 1. Vial Labels
 - a. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
 - b. Revise the proposed proprietary name throughout the labels and labeling to title case (i.e., Vizamyl).

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

2. Shield Labeling

- a. Ensure the shield labeling complies with recommendations B1a, B1b, and B1c.

If you have further questions or need clarifications, please contact Sandra Rimmel, project manager, at 301-796-2445.

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

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

/s/

KEVIN WRIGHT
03/25/2013

ZACHARY A OLESZCZUK
03/26/2013

CAROL A HOLQUIST
03/26/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

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

Application: NDA 203137

Application Type: New NDA

Name of Drug: VIZAMYL™ (Flutemetamol F 18 Injection)

Applicant: GE Healthcare

Submission Date: October 26, 2012

Receipt Date: October 26, 2012

1.0 Regulatory History and Applicant's Main Proposals

This NME NDA was received on October 26, 2012 and therefore will be reviewed under The Program. GE Healthcare has developed Flutemetamol F 18 Injection, a PET imaging agent for the visual detection of beta amyloid neuritic plaques in the brains of adult patients with cognitive impairment. The CDTL for this NDA is Dr. Lucie Yang and a standard review determination has been made. The action date is Friday, October 25, 2013. PDUFA date is October 26, 2013.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

N/A

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**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).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) 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.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), 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.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “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)”

Comment:

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

/s/

SHARON P THOMAS
12/06/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203137 BLA#	NDA Supplement #:S-000 BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: VIZAMYL (1st Choice), (b) (4) (2nd Choice) (b) (4) (3rd Choice)		
Established/Proper Name: Flutemetamol [F-18] Injection		
Dosage Form: 150 MBq/ML per multidose vial		
Strengths:		
Applicant: GE Healthcare		
Agent for Applicant (if applicable):		
Date of Application: October 26, 2012		
Date of Receipt: October 26, 2012		
Date clock started after UN:		
PDUFA Goal Date: October 26, 2013	Action Goal Date (if different): Fri., October 25, 2013	
Filing Date: December 24, 2012	Date of Filing Meeting: December 3, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1, 505(b)(1)		
Proposed indication(s)/Proposed change(s):Flutemetamol F18 Injection is a radioactive diagnostic agent indicated with positron emission tomography (PET) imaging for the visual detection of amyloid neuritic plaques in the brains of adult patients with cognitive impairment.		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1)	<input type="checkbox"/> 505(b)(2)
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1)	<input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>	<input type="checkbox"/> Priority	
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<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 Other:	<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 benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 101866				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, 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>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><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 Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <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															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><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 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>			<p>X</p>																	

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , 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>		X		

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 checked="" 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)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index : Does the submission contain an accurate comprehensive index?	X			
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:	X			

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

<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)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		X		
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
Forms and Certifications				
<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>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&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>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?				NDA 203137 is provided in electronic format, therefore a field copy is not provided.
<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>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?			X	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>	X			
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			Sponsor is requesting partial waiver for 0-16 y.o.
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>		X		Certifications required by FDCA Sections 505B(a)(3) and (4) are not included. Request will be included in 74-day letter
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			OSE asked sponsor to resubmit b/c it was included in the NDA submission. It was submitted on 11/21/12 as a separate submission.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	YES	NO	NA	Comment
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>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): September 7, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 12, 2012 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 3, 2012

BLA/NDA/Supp #:

PROPRIETARY NAME: VIZAMYL

ESTABLISHED/PROPER NAME: Flutemetamol [F-18] Injection

DOSAGE FORM/STRENGTH: 150 MBq/ML per multidose vial

APPLICANT: GE Healthcare

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Flutemetamol F18 Injection is a radioactive diagnostic agent indicated with positron emission tomography (PET) imaging for the visual detection of amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Thomas	Y
	CPMS/TL:	Lucie Yang	Y
Cross-Discipline Team Leader (CDTL)			Y
Clinical	Reviewer:	Phillip Davis	Y
	TL:	Lucie Yang	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

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Clinical Pharmacology	Reviewer:	Christy John, Ph.D.	Y
	TL:	Gene Williams, Ph.D.	Y
Biostatistics	Reviewer:	Lan Huang, Ph.D.	Y
	TL:	Jyoti Zalkikar, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sally Hargus, Ph.D.	Y
	TL:	Adebayo Laniyonu, Ph.D.	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Ravindra Kasliwal, Ph.D.	Y
	TL:	Ali Al Hakim, Ph.D.	N
	Reviewer:	Robert Mello	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	John Lee	N
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: Organized in the Electronic Common Technical Document (eCTD) format.</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</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"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <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 disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</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
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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>CLINICAL PHARMACOLOGY</p> <p>Comments:</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"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</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>PRODUCT QUALITY (CMC)</p> <p>Comments:</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><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: 74 day comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</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

<u>CMC Labeling Review</u>	
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority:	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 19, 2013	
21 st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<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"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<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.

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

/s/

SHARON P THOMAS
12/04/2012