

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204677Orig1s000**

**OTHER REVIEW(S)**

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

<b>Product Title<sup>1</sup></b>	<b>Neuraceq™ (Florbetaben F18 Injection) for intravenous use</b>
Applicant	Piramal Imaging SA
Application/Supplement Number	NDA 204677
Type of Application	Original Submission
Indication(s)	For Positron Emission Tomography (PET) imaging of the brain to estimate $\beta$ -amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline
Office/Division	ODE IV/DMIP
Division Project Manager	Sharon Thomas
Date FDA Received Application	December 21, 2012
Goal Date	March 21, 2014
Date PI Received by SEALD	March 13, 2014
SEALD Review Date	March 14, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **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:** This item does not apply to the specific PI under review (**not applicable**).

# Selected Requirements of Prescribing Information

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

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

**Comment:** *Left margin is < 1/2 inch; top margin is > 1/2 inch. Should be 1/2 inch margins on all sides.*

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

**Instructions to complete this item:** If the length of the HL is one-half page or less, 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 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” 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:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:** *There should be white space before the Indications and Usage heading in HL. There should be no white space between the product title and initial U.S. approval. There should be white space between the Patient Counseling Information statement and the revision date.*

## Selected Requirements of Prescribing Information

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

*Comment:*

- YES** 7. Section headings must be presented in the following order in HL:

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

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

*Comment:*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

*Comment:*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

*Comment:*

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S.**

## Selected Requirements of Prescribing Information

Approval:” followed by the **4-digit year**.

**Comment:** *Insert 4-digit year (i.e., 2014), not "YYYY."*

### Boxed Warning (BW) in Highlights

**N/A** 12. All text in the BW must be **bolded**.

**Comment:**

**N/A** 13. The BW 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 and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

**Comment:**

**N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

**Comment:**

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

**Comment:**

### Recent Major Changes (RMC) in Highlights

**N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

**Comment:**

**N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

**Comment:**

**N/A** 18. The RMC 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 in Highlights

**YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:**

### Dosage Forms and Strengths in Highlights

## Selected Requirements of Prescribing Information

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. 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 in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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 in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Insert revision date, not "MM/YYYY." If approved in March, revision date will be 3/2014.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:* Subsection heading 5.1, the word "other" should begin with a capital "O"(i.e., Other, not other). Also update the word "other" to be "Other" in FPI subsection heading 5.1.
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:***

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

## Selected Requirements of Prescribing Information

***Comment:*** In the *CLINICAL STUDIES* section (3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> paragraphs), cross reference to section, not subsection heading. The cross reference should be the following: [see Dosage and Administration (2.4), not [see Image Display and Interpretation (2.4)].

- N/A** 34. 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

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

***Comment:***

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

***Comment:***

- N/A** 37. The BW 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 and ACUTE HEPATIC FAILURE**”).

***Comment:***

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

***Comment:***

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are 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 practice.”

***Comment:***

- N/A** 40. When postmarketing adverse reaction data are 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:***

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A** 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

- [text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 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
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEANNE M DELASKO  
03/17/2014

ERIC R BRODSKY  
03/17/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

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

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

Memorandum

**Date:** February 10, 2014  
**To:** Sharon Thomas, Regulatory Project Manager  
Division of Medical Imaging Products (DMIP)  
**From:** Emily Baker, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)  
**Subject:** NDA 204677  
OPDP Labeling Comments for Neuraceq (Florbetaben F18 Injection)

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OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on January 28, 2014, for Neuraceq (Florbetaben F18 Injection) (Neuraceq). Our comments on the PI and carton and container labeling are based on the proposed labeling at the following location: <\\CDSESUB1\evsprod\NDA204677\204677.enx>.

**Carton and Container Label**

OPDP has no comments on the proposed carton and container labeling at this time.

**Package Insert**

OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed material.

If you have any questions, please contact Emily Baker at 301.796.7524 or [emily.baker@fda.hhs.gov](mailto:emily.baker@fda.hhs.gov).

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EMILY K BAKER  
02/10/2014

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: August 29, 2013

TO: Sharon Thomas, Regulatory Project Manager  
Brenda Ye, M.D., Clinical Reviewer  
Alex Gorovets, M.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: Janice Pohlman, M.D., M.P.H., Team Leader  
Susan D. Thompson, M.D., Team Leader  
for Kassa Ayalew, 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 204-677

APPLICANT: Piramal Imaging, S.A.

DRUG: Florbetaben (BAY 94-9172, no trade name)

NME: Yes

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

  

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: February 6, 2013

INSPECTION SUMMARY GOAL DATE: August 30, 2013

DMIP ACTION GOAL DATE: December 20, 2013

PDUFA DUE DATE: December 21, 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. Most AD cases occur sporadically, but rare familial mutations are known to be genetically inherited (autosomal dominant). 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, beta-amyloid peptide fibrils (beta-amyloid) appear to be important to its pathogenesis; accumulation of beta-amyloid is the hallmark of AD and a key confirmatory histopathologic criterion at autopsy. Clinical diagnosis of AD is often inaccurate and proven incorrect at autopsy.

Florbetaben is a new molecular entity (**NME**) similar to Amyvid<sup>®</sup> (florbetapir F-18), a product in the same pharmacologic class and currently approved in the US for the same clinical indication. The safety and efficacy of florbetaben for use as a PET imaging agent (as claimed by the sponsor) are supported by two pivotal studies, original interventional Study 14595 and pooled read Study 16034. Both studies were initially sponsored by Bayer HealthCare, Inc. (**Bayer**), and Piramal Imaging, SA (**Piramal**) acquired the product from Bayer shortly before filing this New Drug Application (**NDA**).

For both pivotal studies, the efficacy data were collected by a contract research organization (**CRO**) by reading the images obtained at clinical investigator sites where the study conduct included the administration of the study medication followed by PET imaging. The florbetaben PET images were sent (electronically) to the central core imaging laboratory CRO for blinded interpretation. In analyzing the image read results, histopathology (assessed at a central pathology laboratory CRO) served as the standard of truth (**SOT**). The two pivotal studies audited for this NDA are described further below.

### Study 14595

*An open-label, non-randomized study to evaluate the efficacy and safety of BAY 94-9172 (ZK 6013443) positron emission tomography (PET) imaging for detection/exclusion of cerebral beta-amyloid when compared to postmortem histopathology*

This Phase 3, multi-center, non-randomized, single-dose study was conducted over 30 months (November 2009 to May 2012) in 218 subjects at 15 study centers in Australia (one center), France (two centers), Germany (two centers), Japan (three centers), and US (seven centers).

- The primary study objective was to determine the sensitivity and specificity of florbetaben PET in detecting cerebral beta-amyloid using histopathology as the SOT.
- This study was open-label with respect to study drug administration (single-group, non-randomized) and blinded with respect to image interpretation. In reading MRI and florbetaben PET images, the readers were blinded to the clinical status of the corresponding subjects.

### **Subjects and Inclusion Criteria**

- Study subjects were recruited from hospices, dementia centers, and private practice centers to include the full spectrum of probability for cerebral beta-amyloid deposition, from non-demented volunteers (**NDVs**) to AD or Dementia with Lewy Bodies (**DLB**).
- To support determination of specificity, ten cognitively normal young healthy volunteers (**HVs**) between 21 and 40 years of age were also recruited into the study.
- Able to comply with study requirements and provide informed consent (or assent), specifically including the consent to perform post-mortem brain examination in case of death
- Age  $\geq$  21 years; for women, no child-bearing potential or a negative urine pregnancy test on the day of florbetaben injection

## Study Visits and Procedures

- Subjects visited the study center for screening, PET imaging, and 24-hour safety follow-up. Subjects were interviewed by phone at one week to complete the safety follow-up.
- Screening visit (up to 12 weeks prior): written informed consent for participation in the study (mandatory), genetic screening (optional), and in case of death, post-mortem brain examination (mandatory, except for HVs); clinical history (medical, neurologic, and surgical) and neuropsychiatric/psychometric evaluations
- Brain MRI prior to florbetaben PET (up to six months prior to florbetaben PET acceptable if performed according to protocol); single intravenous injection of study drug and florbetaben PET at 90-110 minutes post-injection ( $300 \text{ MBq} \pm 20\%$ ); follow-up visit (20 - 28 hours after study drug) and safety follow-up by phone in seven days.
- To evaluate long-term beta-amyloid deposition in the brain, all subjects were asked to return yearly for three years for repeat MRI and florbetaben PET. The long-term data were not included in the study (available upon request).

## Endpoints and Analyses

- Primary efficacy endpoint: presence or absence of amyloid-beta in any of six brain regions as visualized (regional tracer uptake) by florbetaben PET
  - Co-primary efficacy analyses: sensitivity and specificity of florbetaben PET in visually detecting brain regions with and without beta-amyloid deposition
  - Major secondary analyses: (1) quantitative assessment using standardized uptake value ratio (**SUVR**) by brain regions, and (2) visual assessment at subject level (whole brain) using clinical diagnoses as the reference standard
- Six brain regions: 1 = frontal, 2 = occipital, 3 = hippocampus, 4 = anterior cingulate, 5 = posterior cingulate, and 6 = cerebellum
  - PET and histopathology compared for 180 brain regions (30 brains x 6 regions/brain)
  - 60 brain regions (10 x 6) from 10 HVs with negative SOT (beta-amyloid assumed to be absent)
- Evaluation by majority of three independent blinded readers using brain histopathology as SOT; 95% confidence interval (**CI**) calculated separately for individual and majority reads

## Major Findings

- Majority read by brain region overall (co-primary efficacy endpoints/analyses): sensitivity 77% (95% CI 65 - 89%) and specificity 94% (95% CI 89 - 100%)
- Florbetaben PET performance by brain region:
  - Best in Region 5 (posterior cingulate): sensitivity 77%, specificity 100%
  - Worst in Region 3 (hippocampus): sensitivity 67%, specificity 60%
- Safety: 216 subjects given florbetaben (137 AD, 5 DLB, 31 other dementias, 32 NDVs, and 11 HVs); adverse events (**AEs**) temporally related to the study drug injection (within 7 days) were seen in 64 subjects (30%)
  - AEs were typically non-serious and mild-moderate in severity: injection site pain/reactions, headache, abnormal liver function, skin eruption/rash, fever, and hypotension
  - Serious AEs (**SAEs**) and deaths were considered to be due to the progression and/or complication of underlying disease, and unrelated to the study medication.

### Study 16034 (Pooled Read)

*A non-interventional study to assess the reliability, reproducibility and efficacy of the florbetaben  $\beta$ -amyloid PET scan visual assessment method as trained via a computer-(Web)-based training tool*

This pooled re-read study was performed at (b) (4). The primary study objective was to evaluate the reproducibility (inter-reader agreement) of florbetaben PET imaging (visual assessment) in a study population that approximates clinical use. Four hundred sixty one (461) florbetaben PET scans were selected from earlier florbetaben studies (Phases 1 - 3, including the Phase 3 histopathology study) to represent the full spectrum of dementia (HVs, NDVs, MCI, AD, other).

#### **Inclusion Criteria**

Florbetaben PET images from previous studies (Phases 1 - 3) to include the full range of dementia:

- **Clinical dementia:** probable/possible (mild to moderate) AD, fronto-temporal lobe dementia (**FTLD**), vascular dementia (**VaD**), DLB, Parkinson's disease dementia (**PDD**)
- **Non-demented subjects:** MCI, young (< 40 years) and elderly (> 55 years) cognitively normal HVs
- From Phase 3 histopathology study: 55 autopsy cases (clinically demented and non-demented) and 10 HVs as negative controls

#### **Study Procedures**

- Florbetaben PET images from original 461 cases and 46 re-read cases (10% of original) were pooled and randomized for visual assessment by five independent blinded readers.
- As intended in the eventual clinical setting (post-approval), the readers were trained using a web-based training tool.
- For each case, the presence or absence of beta-amyloid was assessed at the subject (whole brain) level using the brain amyloid plaque load (**BAPL**) visual scoring algorithm (BAPL score of 1 is normal, scores of 2 or 3 are abnormal).

#### **Endpoints and Analyses**

- Primary: BAPL scores and inter-reader agreement by BAPL scores at the subject level (whole brain) across the five blinded readers (kappa statistic)
- Secondary:
  - Inter-reader agreement for each combination of reader pairs (ten pairs), and (2) intra-reader agreement based on the re-reads of 46 images (10% of originals) for each (five) blinded readers
  - Sensitivity and specificity, using: (1) histopathology (54 autopsy cases from Study 14595) and 10 HVs (clinical history) as SOT, and (2) histopathology only as SOT (without HVs)

#### **Major Findings**

- Reader agreement (kappa statistic, BAPL scores by visual assessment):
  - Inter-reader: 0.79% (0.75-0.82); 0.68 (0.619-0.74, readers 2/5) and 0.87 (0.82-0.91, readers 1/3)
  - Intra-reader: 0.82% (0.66-0.99, reader 1) and 0.96% (0.87-1.0, reader 4)
- Diagnostic performance (histopathology SOT):
  - With HVs: sensitivity of 90% (81-99, readers 1/2), 88% (77-98, readers 3/4), or 78% (65-90, reader 5); specificity range of 63% (43-82, reader 3) to 92% (81-100, reader 5)
  - Without HVs: sensitivity identical to that with HVs; specificity lower (4 readers) or higher (one reader) than with HVs

## II. INSPECTIONS

Four sites were inspected in support of this NDA review: three CRO sites (imaging, pathology, and study monitoring CROs) and one representative clinical investigator site:

- For the two (both) pivotal studies, (b) (4) served as the central imaging laboratory (imaging CRO). For the original florbetaben PET-histopathology correlation Study 14595, (b) (4) served as the pathology laboratory where histopathology was assessed (pathology CRO).
- Oversight monitoring of study conduct was performed by both the sponsor (for the pooled imaging Study 16034) and by (b) (4) (monitoring CRO for the PET-histopathology correlation Study 14595). Study conduct monitoring was audited at (b) (4) using the study records available on-site at (b) (4) (for Study 14595) and sent by the sponsor (for Study 16034).
- Osama Sabri: Among the clinical sites that participated in the original florbetaben PET-histopathology correlation Study 14595, this was the largest site and had the greatest number (three) of major protocol deviations.

	Inspected Entity	Studies and Subjects	Inspection Dates	Inspection Outcome
1	(b) (4) (image read CRO)	Study 16034 (pooled read) 461 subjects Study 14595 (original pivotal) 218 subjects	(b) (4)	Pending Preliminary NAI
2	(b) (4) (pathology laboratory CRO)	Study 14595 218 subjects and PET images 55 brain autopsies	(b) (4)	NAI
3	Osama Sabri, M.D. Leipzig, Germany (clinical investigator)	Study 14595, Site 10001 36 subjects	May 13 - 17, 2013	VAI
4	(b) (4) (study monitoring CRO)	Study 14595 218 subjects and PET images 55 brain autopsies Study 16034 461 subjects from previous studies, 507 PET images	(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)

Pending: Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final inspection report has not been received from the field office and OSI's complete review of the final inspection report remains pending as of this clinical inspection summary.

**1.** [REDACTED] (b) (4)**a.** What was inspected:

- Compliance with good clinical practice (**GCP**) regulations, study protocols, standard operating procedures (**SOPs**), and imaging charters (with emphasis on the integrity of the study blind in interpreting PET images)
- Data verification for Study 14595:
  - For the region reads, CRFs were sampled and compared with the NDA listings for 36 records (3 x 2 x 6; three readers, two different regions per reader, six subjects): (1) Reader 1, Regions 1 and 2, (2) Reader 2, Regions 3 and 4, and (3) Reader 3, Regions 5 and 6.
  - For the subject reads, 12 records were randomly selected from the sample above, six from Reader 1 and three each from Readers 2 and 3.
- Data verification for Study 16034: 25 records (5 x 5; five records each for five blinded readers) were arbitrarily selected to cover the entire the dataset.

**b.** General observations:

- The readers in Study 16034 were trained on interpreting the florbetaben PET images using only the web-based training tool. MRIs were provided to the readers only for the regional reads in Study 14595. The MRIs were not provided in Study 16034 (pooled read) or for the subject level reads in Study 14595.
- No significant deficiencies were observed and a Form FDA 483 was not issued. For both studies, all audited data (and images) matched the NDA data listings (time, date, results, region, and reader number). All CRFs were signed as complete by the reader and the proctor. Electronic data controls and test article accountability appeared to be adequate.

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

Note: These observations are based on preliminary communications with the field investigator. The final inspection report has not been received and the inspection outcome remains pending.

**2.** [REDACTED] (b) (4)**a.** What was inspected:

- Compliance with GCP: Study protocol and applicable SOPs in preparing histopathology slides for SOT interpretation by the Consensus Panel, including records review of 45 Core Pathology Worksheets.
- Role of CRO and process flow: There were no study data to be verified at this CRO site. Tissue blocks received from various study sites were processed at this central pathology laboratory to produce histopathology slides using standardized methods for quality control and quality assurance.
- Relationship to SOT data generation: The slides were sent (periodically) to a central location elsewhere ([REDACTED] (b) (4)), where a Consensus Panel of three blinded neuropathologists convened (periodically) to interpret the slides and generate the SOT data.

**b.** General observations:

- No significant deficiencies were observed and a Form FDA 483 was not issued. Adherence to GCP in preparing the histopathology slides appeared to be adequate, as did study monitoring by Bayer HealthCare (former sponsor) and [REDACTED] (b) (4) (monitoring CRO).

- Two isolated deficiencies were discussed verbally (not cited on Form FDA 483, inspector discretion). These items are not expected to affect the quality of the histopathology slides or otherwise influence their interpretation by the Consensus Panel to generate the SOT data.
  - Two histology technicians were retrospectively added to the delegation of authority log (back-dated entries). Further, their training on the study protocol was not documented.
  - Ten of the 45 Core Pathology Worksheets reviewed were incomplete for the section intended to show the number of slices on the tissue block needed to obtain the tissue section mounted on the glass slide.

c. Assessment of data integrity:

Endpoint study data were not generated at this pathology CRO site. From tissue blocks obtained from various study sites, tissue sections were cut, stained, and mounted on glass slides using standardized methods to facilitate their accurate interpretation. Deficiencies with the potential to adversely affect the reliability of the study data (histopathology SOT) were not observed.

### 3. Osama Sabri, M.D.

a. What was inspected:

- Audit of Study 14595 for site compliance with the study protocol, good clinical practice regulations, and applicable standard operating procedures
- Sponsor and IRB monitoring, financial disclosures, test article accountability, and subject data verification
- The study was on-going at the time of inspection (expected completion in February 2014). At this site, 43 subjects were screened (including seven healthy volunteers), 36 subjects were enrolled, and eight subjects completed the study (as of the inspection date).
- Records for all enrolled subjects were reviewed in detail to verify subject eligibility, informed consent, on-site endpoint (brain amyloid plaque load score) and adverse event data, protocol deviations, and subject discontinuations.

b. General observations:

- A single-item Form FDA 483 was issued for deviating from the study protocol in performing long-term follow up imaging: for four Subjects 2001, 2002, 2005, and 2009, MRI was not performed at one-year follow up, in deviation from the recommendation specified in the protocol (whenever feasible).
- The following additional deficiency observations were verbally discussed (not cited, inspector discretion):
  - One study personnel that participated in study drug manufacturing (and maintaining records related to manufacturing, including drug accountability records) was not named on the delegation of authority log. This person was also not trained on the protocol until well after the study was initiated.
  - The information on source records (accurate) did not always match the corresponding information on the CRF (inaccurate):

Subject 4003: Discontinuation date of concomitant medication Delix not recorded on CRF

Subject 1012: PET imaging dates on source records and CRF discrepant by one day

Subject 2009: Frontal cortex tracer binding pronounced (source) versus none (CRF)

- Other than as noted above, all audited study data were verifiable and matched among source records, CRFs, and NDA data listings. IRB oversight and study monitoring (by (b) (4)) appeared to be adequate. All subjects signed the informed consent document. Source records were complete and well-maintained.

*Reviewer's Comments:*

- All observed deficiencies appear isolated, minor, and unlikely to be significant to the overall study outcome. Although specified in the protocol (encouraged whenever feasible), the importance of (no) long-term follow up MRI is unclear.
- Of the deficiencies observed (cited or verbal), the most significant may be the inaccurate reporting of one (frontal cortex) tracer uptake value for one subject. As one datum for a minor secondary endpoint (the only efficacy endpoint obtained on-site), this apparent isolated transcription error is not expected to impact the study outcome.

c. Assessment of data integrity: Data from this site appear reliable as reported in the NDA.

4. (b) (4)

a. What was inspected:

- Audit of the oversight for Studies 14595 and 16034: (1) adherence to the study protocols, image review charters (IRCs), standard operating procedures (SOPs) and good clinical practice (GCP) regulations; (2) database controls and image/data management
- Data verification: consistency of case report forms (CRFs), PET images interpretation data (source records), and NDA data listings
  - Study 14595: visual amyloid detection, standard tracer uptake value ratio, adverse events, image randomization, protocol deviations, and subject discontinuations
  - Study 16034: brain amyloid plaque load scores, reader agreement, and accuracy of florbetaben PET (sensitivity and specificity)

b. General observations:

- No significant deficiencies were noted and a Form FDA 483 was not issued. Three deficiencies for Study 14595 were verbally discussed (inspector discretion):
  - For one subject, the consensus read was performed by a panel of two readers, and not three as specified in the protocol
  - No documentation of secondary monitoring (monitoring of monitoring) during the initial site visit, as specified in the SOP entitled *Training Requirements for CRAs*
  - An apparent delay of ten weeks in documenting the signed review of one monitoring report, in violation of SOP entitled *Trial Site Monitoring*.

c. Assessment of data integrity: The observed deficiencies appear to be minor, isolated, and unlikely to impact study quality. The study data appear reliable as reported in the NDA.

Note: (b) (4) was inspected in lieu of the originally planned inspection of the sponsor Piramal. (b) (4) had monitored Study 14595, an original PET-histopathology correlation study in which the diagnostic accuracy of florbetaben PET was determined (one of two pivotal studies). To facilitate the audit of the sponsor's oversight of Study 16034 (second pivotal study), the sponsor shipped the study records for concurrent review at inspection of (b) (4). In Study 16034, PET images from previous studies were pooled and re-read to determine the effectiveness of an electronic reader training tool.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

For the two pivotal studies supporting this NDA, four major study areas were identified and four representative sites were inspected (one site per area): (1) subject selection and performance of florbetaben PET, (2) interpretation of florbetaben PET images, (3) histopathology SOT determination, and (4) study monitoring and oversight. Inspectional observations were limited to minor isolated deficiencies. The study data appear reliable as reported in the NDA.

In auditing how the histopathology SOT data were determined, the histopathology laboratory at (b) (4) was selected for inspection. At this site, there were no major study data to be verified; from tissue sampled at outside centers, histopathology slides were produced for microscopic interpretation by a Consensus Panel that convened periodically (elsewhere) to determine the SOT. The sponsor may be queried about how this panel functioned (charters and/or SOPs) and what records are available for review.

Note: The final inspection report for (b) (4) has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division if the final classification changes or if additional observations of clinical or regulatory significance are discovered.

{See appended electronic signature page}

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

CONCURRENCE:

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08/29/2013

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08/29/2013

SUSAN D THOMPSON  
08/29/2013

**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: July 16, 2013

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

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

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

Drug Name and Strength(s): Neuraceq (Florbetaben 18F) Injection  
50 MBq to 5,000 MBq per mL (1.35 mCi to 135 mCi per mL)

Application Type/Number: NDA 204677

Applicant/sponsor: Piramal Imaging, SA

OSE RCM #: 2013-20

\*\*\* 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 Neuraceq NDA 204677 for areas that can contribute to medication errors.

### 1.1 PRODUCT INFORMATION

The following product information is provided in the December 21, 2012 NDA submission.

- Intended pronunciation: Neu'rah sek
- Active Ingredient: Florbetaben F-18
- Indication of Use: indicated for the detection of beta-amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline
- Route of Administration: Intravenous
- Dosage Form: Solution for Injection
- Strength: 50 to 5000 MBq per mL (1.35 to 135 mCi per mL)
- Dose and Frequency: Administer 300 MBq as a slow intravenous push (max volume: 10 mL)
- How Supplied: 30 mL glass vials (b) (4)
- Storage: Store at room temperature (25°C)
- Container and Closure Systems: 30 mL glass vial with (b) (4) gray stopper. The stopper is fixed with a flanged closure made of an aluminum shell.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS databases for Amyvid medication error reports because this is a recently approved imaging agent and any errors identified with Amyvid labels and labeling would be relevant to this review. We also reviewed the Neuraceq labels and package insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

The FAERS database search did not identify any cases.

<b>Table 1: FAERS Search Strategy</b>	
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,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 21, 2012 (Appendix B)
- Carton Labeling submitted December 21, 2012 (Appendix C)
- Insert Labeling submitted December 21, 2012

Our review identified areas of needed improvement. See Section 4 for recommendations.

## 3 CONCLUSIONS

DMEPA concludes that the proposed container label, shield and prescribing information can be improved to increase the prominence of important information on the label to promote the safe use of the product clarify information.

## 4 RECOMMENDATIONS

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

### A. Comments to the Division

#### 1. Section 16 How Supplied

- a. Revise the statement “ (b) (4) so that it is consistent with the container label and shield labeling. More specifically, the storage conditions should read, Store at (b) (4) room temperature 25°C (77°F); excursions permitted to (b) (4)

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

B. Comments to the Applicant

1. Vial Labels

- a. Delete (b)(4) appearing at the top of the label to create space for the proprietary name and established name. As presented the (b)(4) around the label are more prominent than the most important information, the proprietary name and established name.
- b. Revise the container label so the proprietary name and established name are only presented once. (b)(4)
- c. Ensure the established name appears at ½ the font size as of the proprietary name taking into account all pertinent factors, including font size, typography, layout, contrast, coloring and other printing features.
- d. Ensure the proposed proprietary name appears in title case (i.e. Neuraceq) on the container the labels and carton labeling.
- e. Revise the statement (b)(4) to read “For Intravenous Use Only”, and increase the prominence of this statement.
- f. Revise the statement (b)(4)” to read “Sterile” and “Rx Only” in a stacked format. As presented this statement does not convey sensible information to the end user.

2. Shield Labeling

- a. Ensure the shield labeling complies with recommendations B1a, through B1f.

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

## **APPENDICES**

### **APPENDIX A. DATABASE DESCRIPTIONS**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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KEVIN WRIGHT  
07/16/2013

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CAROL A HOLQUIST  
07/16/2013

# **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:** 204677

**Application Type:** NME NDA, Type 1

**Name of Drug:** Florbetaben [F-18] Injection

**Applicant:** Piramal Imaging SA (c/o CBR International – US Agent)

**Submission Date:** December 21, 2012

**Receipt Date:** December 21, 2012

## **1.0 Regulatory History and Applicant's Main Proposals**

This NDA proposes florbetaben for the detection of beta-amyloid in the brain, and to assist in the diagnosis of Alzheimer's disease. Florbetaben was developed by Bayer HealthCare Pharmaceuticals Inc. ("Bayer") under IND78, 868. In December 2012, Bayer submitted a Change of Sponsor notification to IND 78,868 informing FDA that Piramal had become the new Sponsor.

FDA sent an SPA "No Agreement" letter on December 23, 2010. An EOP2/Guidance meeting was held on June 1, 2011 and a pre-NDA meeting was held on August 24, 2012. The NDA will be reviewed under "The Program" of PDUFA V, as a standard review with a PDUFA date of December 21, 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**

Selected Requirements of Prescribing Information (SRPI) format deficiencies were identified in the review of this PI. The two SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 8, 2013.

## 5.0 Appendix

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

**YES** 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:*

## 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

**NO** 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: *Sponsor to include pharmacologic class "radioactive diagnostic agent"*

### Dosage Forms and Strengths

## Selected Requirements of Prescribing Information (SRPI)

- YES** 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

- N/A** 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

- N/A** 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:

**YES**

## 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.

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

## Selected Requirements of Prescribing Information (SRPI)

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

**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:**

- NO** 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:**

- YES** 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

- YES** 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:** Sponsor to include the language above in the PI

- 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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON P THOMAS  
02/28/2013

## 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 # 204677 BLA#	NDA Supplement #:S-000 BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name Proposed: Neuraceq Established/Proper Name: Florbetaben for Injection Dosage Form: IV Strengths: 50 – 5000 MBq (1.35 – 135 mCi) per mL		
Applicant: Piramal Imaging S.A. Agent for Applicant (if applicable): c/o CBR International- US Agent)		
Date of Application: December 21, 2012 Date of Receipt: December 21, 2012 Date clock started after UN:		
PDUFA Goal Date: December 21, 2013	Action Goal Date (if different): Fri., December 20, 2013	
Filing Date: February 19, 2013	Date of Filing Meeting: January 29, 2013	
Chemical Classification: 1, (original NDAs only) Type 1, 505(b)(1)		
Proposed indication(s)/Proposed change(s): Florbetaben is indicated for the detection of $\beta$ -amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<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): <b>IND 78,868</b>				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If 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: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>			X	
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	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><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></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:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></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><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></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>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>			<p>X</p>																	

<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [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		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>		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?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> 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			

1

<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)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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"> <li>If yes, were all of them submitted on time?</li> </ul>			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			
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature 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			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature 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>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	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>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> 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&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?				NDA 204677 is provided in electronic format, therefore a field copy is not needed.
<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>				
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>				
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b><u>PREA</u></b>	X			
Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			Sponsor is requesting full waiver for 0-17 y.o.
<b>If a request for full waiver/partial waiver/deferral is included</b> , 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
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Yes. Included in the NDA submission on 12/21/12.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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		
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

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

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request 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			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined?	X			

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> June 1, 2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> August 24, 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> December 21, 2010		X		SPA -No Agreement
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 19, 2013

**BLA/NDA/Supp #:** NDA 204677

**PROPRIETARY NAME:** Neuraceq

**ESTABLISHED/PROPER NAME:** Florbetaben for Injection

**DOSAGE FORM/STRENGTH:** IV, Injection / 50 – 5000 MBq (1.35 – 135 mCi) per mL

**APPLICANT:** Piramal Imaging S.A.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Florbetaben is indicated for the detection of  $\beta$ -amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer’s disease and other causes of cognitive decline.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Sharon Thomas	Y
	CPMS/TL:	Kaye Kang	
Cross-Discipline Team Leader (CDTL)	Alex Gorovets		Y
Clinical	Reviewer:	Brenda Ye	Y
	TL:	Alex Gorovets	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	

Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Lan Huang	Y
	TL:	Jyoti Zalkikar	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sunny Awe	Y
	TL:	Adebayo Laniyonu	
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:	Ann Marie Russell	Y
	TL:	Eldon Leutzinger	Y
	Reviewer:	Erika Pfeiler	Y
	TL:	Bryan Riley	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	TBD	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

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

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b> Organized in the Electronic Common Technical Document (eCTD) format.</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> </ul>	<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"> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

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

<b><u>CMC Labeling Review</u></b>	
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Alex Gorovets, CDTL  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): May 15, 2013  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): Mid-Cycle Communication Meeting May 21, 2013, Labeling to Piramal  <b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<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
<b>ACTIONS ITEMS</b>	
<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"> <li>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)</li> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<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: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<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.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON P THOMAS  
02/19/2013