

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204677Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204677

SUPPL #

HFD # 160

Trade Name Neuraceq

Generic Name florbetaben f18 injection

Applicant Name Piramal Imaging SA

Approval Date, If Known 3/21/2014

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO



interest provided substantial support for the study?

Investigation #1  
!  
! YES  NO   
! Explain: ! Explain:

Investigation #2  
!  
! YES  NO   
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

---

Name of person completing form: Sharon Thomas  
Title: Project Manager  
Date: 3/3/2014

Name of Office/Division Director signing form: Libero Marzella, MD, PhD  
Title: Division Director (acting)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/  
-----

SHARON P THOMAS  
03/05/2014

LIBERO L MARZELLA  
03/05/2014

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 204677 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Medical Imaging Products PDUFA Goal Date: 12/21/13 Stamp Date: 12/21/12

Proprietary Name: Neuraceq

Established/Generic Name: (Florbetaben F 18 Injection)

Dosage Form: Injection solution

Applicant/Sponsor: Piramal Imaging SA

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** 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.

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: 204677 Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

**justification):**

## # Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

## \* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

## † Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

## Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

---

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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

/s/  
-----

SHARON P THOMAS  
03/06/2014



## Debarment Certification

Bayer HealthCare Pharmaceuticals hereby certifies under Section 306(k)(1) of the Federal Food and Drug Cosmetic Act that it did not and will not use in any capacity, the services of any person debarred under Section 306 of the FD&C Act in connection with NDA 204,677.

Date:

November 21, 2012

Signature:

Maria C. Garrigan

Maria C. Garrigan  
Director, GRA TA Specialty Medicine  
Bayer HealthCare Pharmaceuticals

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 204-677	NDA Supplement # n/a BLA Supplement #	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Neuraceq Established/Proper Name: Florbetaben F 18 Dosage Form: Injection		Applicant: Piramal Imaging SA Agent for Applicant (if applicable): CBR International Corp.
RPM: Sharon Thomas		Division: DMIP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>3/21/2014</u></li> </ul>		<input checked="" type="checkbox"/> AP 3/19/2014 <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): 1  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 03/21/2014
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included 3/18/2014
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included 3/18/2014
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	4/10/2013 4/10/2013
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 2/28/2013 DMEPA: <input type="checkbox"/> None 7/16/2013 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 2/10/2014 SEALD: <input type="checkbox"/> None 3/17/2014 CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	2/19/2013- RPM , Nonclinical: 1/29/2013, Microbiology: 1/30/2013 CMC: 2/12/2013, Clinical Pharmacology: 2/18/2013, Clinical: 2/18/2013, Statistics: 2/19/2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo ( <i>indicate date</i> )	
○ If yes, OC clearance for approval ( <i>indicate date of clearance communication</i> )	<input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	Pediatric Page: 3/6/2013
• Date reviewed by PeRC <u>7/10/2013</u> If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	3/7/2014, 3/5/2014, 3/3/2014, 2/28/2014, 2/20/2014 2/11/2014, 1/16/2014, 12/13/2013 <b>12/13/2013 (Review Extension-Major Amendment)</b> 11/27/2013, 11/15/2013, 11/8/2013, 10/23/2013, 10/18/ 2013, 10/10/2013,10/7/2013, 8/29/2013 8/26/2013, 8/23/2013, 8/21/2013, 8/12/2013, 7/30/2013, 7/25/2013, 7/1/2013, 6/24/2013, 6/21/2013, 6/14/2013, 5/17/2013, 4/30/2013 4/17/2013, 4/3/2013 (2), 3/26/2013 2/7/2013, 1/29/2013 1/18/2013, 12/31/2012
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	12/3/2013, 11/21/2013,10/8/2013, 6/14/2013, 3/5/2013, 2/1/2013
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 8/24/2012
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• Mid-cycle Communication ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A 5/21/2013
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A 9/10/2013
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/19/14
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/19/14, 2/28/2014 & 11/27/2013
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/28/2013
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None

<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)	1/31/2014 & 8/23/2013 , 2/18/2013 (filing)
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	See Clinical Review dated 8/23/2013, page 13.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</li> <li>• REMS Memo(s) and letter(s) (indicate date(s))</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</li> </ul>	<input type="checkbox"/> None 2/13/2014 & 8/30/2013
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input type="checkbox"/> None requested 8/14/2013, 8/28/2013 (2 letters), <u>8/29/2013</u>
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 1/31/2014 & 8/23/2013 (2/19/2013 - filing)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 1/31/2014 & 8/22/2013 (2/18/2013 - filing)
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> 3/10/2014
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/22/2013 (1/29/2013- filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> 3/18/2014
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/10/2014, 12/13/2013 & 8/23/2013 (2/12/2013- filing)
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed 8/13/2013 (1/30/2013- filing)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See CMC Review 8/23/2013, page 97.
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i> )	Date completed: 12/12/2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review)

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/  
-----

SHARON P THOMAS  
03/24/2014

**From:** Thomas, Sharon  
**Sent:** Friday, March 07, 2014 12:59 PM  
**To:** Kevin Hennegan ([khennegan@cbrintl.com](mailto:khennegan@cbrintl.com))  
**Cc:** Jeanne Novak ([jnovak@cbrintl.com](mailto:jnovak@cbrintl.com))  
**Subject:** Neuraceq PI

Dear Kevin,

Attached is the Neuraceq package insert (PI) for NDA 204677 based on FDA review. In order to facilitate negotiations, we request that you respond by close of business, Tuesday, March 11, 2014.

Please review the comments (green), specifically where Piramal agrees with the labeling and accept the tracked changes. Where Piramal does not agree with the labeling revisions, please provide your comments and proposed language (shown in tracked-changes). Also, please review the document for formatting, spacing and margins.

Please confirm receipt of this e-mail correspondence. If you have any questions, please feel free to contact me.

Kind regards,

Sharon

\*\*\*\*\*

**Sharon Thomas**  
**Senior Regulatory Project Manager**  
**Division of Medical Imaging Products | Project Management Staff**  
**Ph: 301-796-1994 (O)**  
**Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)**

(b) (4)

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

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

/s/  
-----

SHARON P THOMAS  
03/07/2014

**From:** Thomas, Sharon  
**Sent:** Wednesday, March 05, 2014 2:20 PM  
**To:** 'Kevin Hennegan'  
**Cc:** Jeanne Novak  
**Subject:** RE: NDA 204677/ Neuraceq / CMC IR

Dear Kevin,

With regards to the PI, vial and shield labels, we have the following comments/request for information:

1. Provide dimensions of the vial label (inches) and the minimum font size.
2. Revise the excursion temperature to (b) (4) degrees C in the package insert, vial and shield label.

Please feel free to contact me if you have any questions.

\*\*\*\*\*

Sincerely,

Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products | Project Management Staff  
Ph: 301-796-1994 (O)  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
03/05/2014

**From:** Thomas, Sharon  
**Sent:** Monday, March 03, 2014 4:02 PM  
**To:** Kevin Hennegan (khennegan@cbrintl.com)  
**Cc:** Jeanne Novak (jnovak@cbrintl.com)  
**Subject:** RE: Neuraceq (Florbetaben) PI

Dear Kevin,

Please see the comment below from the statistical reviewer regarding table 8 in the PI:

**\*\*\*\*If the patients are in DLB, FTLD, VaD, PD, DEM, other, or NA groups, they are in "Other Dementias". Please incorporate the appropriate footnotes.**

Other Dementias (n=40)	18	0.65 (0.55, 0.74)	7.5	32.5	60
------------------------	----	----------------------	-----	------	----

Please don't hesitate to contact me if you have any questions.

\*\*\*\*\*

Sincerely,

Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products | Project Management Staff  
Ph: 301-796-1994 (O)  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

**From:** Kevin Hennegan [<mailto:khennegan@cbrintl.com>]  
**Sent:** Monday, March 03, 2014 11:07 AM  
**To:** Thomas, Sharon  
**Cc:** Jeanne Novak  
**Subject:** RE: Neuraceq (Florbetaben) PI

Hi Sharon,

In the draft of the clinical section you provided on 21 February, the footnote to Table 8 stated that Other dementias included "...dementia associated with PD," which would bring the total n for this category to 40. However, the statistical reviewer's response below excludes Parkinson's Disease patients. Should the footnote to Table 8 be revised to exclude PD patients?

Thank you for any additional clarification you can provide.

Best regards,

Kevin

*This electronic transmission (including any and all attachments) is intended solely for the use of the individual or entity to whom it is addressed and may contain information that is privileged and/or confidential. If you are not the intended recipient of this electronic transmission, you are*

*hereby notified that any disclosure, copying or distribution, or the taking of any action in reliance upon the contents of this electronic transmission, is strictly prohibited, and you are further requested to purge this electronic transmission and all copies thereof from your computer system.*

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

/s/  
-----

SHARON P THOMAS  
03/04/2014

**From:** Thomas, Sharon  
**Sent:** Friday, February 28, 2014 2:03 PM  
**To:** Kevin Hennegan (khennegan@cbrintl.com)  
**Cc:** Jeanne Novak (jnovak@cbrintl.com)  
**Subject:** NDA 204677 /Florbetaben/ CMC Information Request

NDA 204677

**INFORMATION REQUEST**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak,

Please refer to your New Drug Application (NDA 204677) for florbetaben, dated and received on December 21, 2012. With regards to the vial and shield labels, we have the following chemistry comments and information requests:

-The text is too small – the operator needs to write data on the label. Also the container label should have the EOS strength.

-The pig label and container label should have the NDC code printed, (b) (4)

-The pig label states manufactured by (b) (4) – this should read IBA, “Corporate Address”

Please provide a MS Word and pdf copy via email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, Tuesday, March 4, 2014 and follow-up with a formal amendment submission to the NDA.

Best regards,  
*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products  
FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
02/28/2014



NDA 204677

**LABELING PMR/PMC DISCUSSION COMMENTS**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to our December 12, 2013, letter in which we notified you of our target date of February 20, 2014 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On January 16, 2014, we received your January 16, 2014, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. Clinical Studies, section 14 of the labeling is still under review and further comments are forthcoming.

Please provide a response to the labeling along with a separate document outlining your proposed modifications with commentary/rationale by Tuesday, February 25, 2014. Also, please accept all edits to the labeling with which you agree.

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BS, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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

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

/s/  
-----

SHARON P THOMAS  
02/20/2014

**From:** Thomas, Sharon  
**Sent:** Tuesday, February 11, 2014 4:30 PM  
**To:** Kevin Hennegan (khennegan@cbrintl.com)  
**Cc:** Jeanne Novak (jnovak@cbrintl.com); Huang, Lan  
**Subject:** Statistical Information Request- NDA 204677- Neuraceq

Hi Kevin,

With regards to Neuraceq, NDA 204677, we have the following statistical information request:

**Please provide the data (xpt file) with the patient id (pid) and the time of PET scan to death (autopsy).**

We kindly request a response via email by 12:00 PM (EST) - Friday, February 14, 2014. Any questions, feel free to contact me.

Thank you.

Sharon

Sharon Thomas, RPM  
Division of Medical Imaging Products  
Office of Drug Evaluation IV, CDER, FDA  
Phone: (301) 796-1994  
Fax: (301) 796-9849  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
02/11/2014



NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to your major amendment received November 22, 2013, containing the complete clinical study report for your Histopathology Read clinical trial, we have the following comments/requests for information regarding text tables 9-1, 9-2, 9-3 and 9-4:

1. In text table 9-4, we note that the blinded readers #2 and #5 had specificity values below the acceptable standard. Please provide an explanation for why these readers are not at the same performance level as the others.
2. Please provide the details on the qualification of readers and the specific aspects on the reading methodology.
3. Please comment on the global (second) read, specifically if it was part of the training program.

In the interest of time, please provide a response by email to Ms. Sharon Thomas, Regulatory Project Manager on Monday, January 20, 2014.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

/s/  
-----

LIBERO L MARZELLA  
01/16/2014



NDA 204677

**GENERAL ADVICE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to your high level summary data from study FBB-01\_01\_13 to the NDA submission dated November 6, 2013 and complete Clinical Study Report in a subsequent submission dated November 22, 2013. We have the following comments to your questions:

1. Does the Agency have any technical comments pertaining to the analyses within the New Read Study (FBB 01\_01\_13) as described in this submission?

**FDA Response:**

**Our review of the study report is ongoing. We have no comments or requests for information at this time.**

2. Does the Agency agree that the efficacy characteristics of florbetaben, as determined in study FBB-01\_01\_13, supp01i approval of florbetaben for the proposed rule-out indication?

**FDA Response:**

**We refer you to our response to question 1.**

3. Does the Agency agree that the efficacy characteristics of florbetaben as determined by the post-hoc analyses presented in sequence 0024, especially the results of the in person trained readers in the extended histopathology subset (n=82 plus 10 HVs), are also supportive of florbetaben approval for the rule-out indication?

**FDA Response:**

**It is premature for us to comment on the indication statement and other aspects of the product labeling. We also refer you to our response to question 1.**

Does the Agency agree that the results of study 312043 (also confirmed in the MCI subset in study 16034) provides additional confidence that florbetaben reliably detects amyloid deposits in the brains of patients likely to undergo testing in clinical practice?

**FDA Response:**

**Please see our responses above.**

4. Are there any substantive review issues that have not been resolved by the recent submission 0031 and our other amendments submitted since the Late Cycle Review meeting (in particular, sequences 0023 , 0024, 0026, 0027, 0028 and 0030?

**FDA Response:**

**We reference your November 22, 2013 submission containing the complete report of Study FBB-01\_01\_13. The study is designed to provide the confirmatory evidence of efficacy of florbetaben F 18 that was lacking in the original NDA submission. We have designated the submission a major amendment and are extending the December 21, 2013 PDUFA regulatory action date to March 21, 2014.**

If you have any questions, please feel free to contact Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994 or via email at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

LIBERO L MARZELLA  
12/13/2013



NDA 204677

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

On November 22, 2013, we received your November 22, 2013, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 21, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 20, 2014. Furthermore, the new planned date for our internal mid-cycle review meeting is January 16, 2014.

If you have any questions, please feel free to contact Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994 or via email at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

LIBERO L MARZELLA  
12/13/2013

**November 25, 2013**  
**Team**  
**Meeting Minutes**  
**NDA 204677**

**Neuraceq (Florbetaben F 18 Injection)**  
**Sponsor - {Piramal Imaging SA}**

---

**Submission Date:** December 21, 2012  
**PDUFA Date:** [REDACTED] <sup>(b) (4)</sup> -March 21, 2014

**Proposed Indication:** Florbetaben is a radioactive diagnostic agent for Positron Emission Tomography (PET) indicated for detection of beta amyloid in the brain, thereby assisting in the differential or confirmatory diagnosis in adult patients who are being evaluated for Alzheimer’s disease (AD) and other causes of cognitive decline.

**Meeting Purpose:** To discuss key findings, issues that could impact approval.

**1. Discussion:**

- **CMC/PT** – In a teleconference held on November 21<sup>st</sup>, FDA asked Piramal to provide justification on [REDACTED] <sup>(b) (4)</sup> impurities which exceeds ICH Q3A qualification limits (0.15%). CMC will consult with PT on the acceptability of those impurities. Piramal agreed to provide the information on November 29<sup>th</sup>.
- **Clinical/ Stats** - On November 22, 2013, Piramal formally submitted the Histopathology Read Report which contains new / additional data for review. The data appears acceptable. DMIP will consider granting the sponsor’s request to extend the review clock. If granted, the new PDUFA goal date is [March 21, 2014](#).
  - Minor concerns with data sets. Stats will submit RPM an information request to convey to sponsor.
  - [REDACTED] <sup>(b) (5)</sup>
- **Compliance** –Facility [REDACTED] <sup>(b) (4)</sup> was issued a FDA-483. Timeline for re-inspection is unknown.
- **Major Amendment Extension**
  - RPM discussed timeline for labeling meetings (Jan – Feb) and need for the internal mid-cycle review meeting proposed under PDUVA V. (Jan)

**2. Milestones/Upcoming Meetings:**

MILESTONES	MILESTONE	MEETINGS
------------	-----------	----------

NDA 204677– Team Mtg -Meeting Minutes

Page 2

	<b>DEADLINES</b>	
Receipt Date	Dec. 21, 2012	
Day 45	Feb. 4, 2013	<a href="#">Filing/Planning Meeting</a> Jan 29
Day 60 (Filing Date)	Feb. 19, 2013	
Day 74 Letter Due	March 5, 2013	
Spon Orientation Mtg		Feb. 4, 2013
Team Meeting		March 5, 2013 [Tues.]
Team /Mid-Cycle Practice		April 11, 2013 [Tues.]
Month 6- Mid-cycle Mtg.	May 21, 2013	<a href="#">Mid-cycle Meeting</a> May 15 [Wed]
Mid-cycle –Communication Mtg.	June 4, 2013	<a href="#">Mid-cycle Comm Mtg</a> May 21 [Tues.]
Team/Labeling Meetings		June 4, 2013 [Tues.]
		June 11, 2013 [Tues.]
		July 8, 2013 [Mon.]
		July 16, 2013 [Tues.]
		Aug 6, 2013 [Tues.]
Send Labeling to Piramal	By Aug, 21, 2013	
Late Cycle Pre-Meeting	Aug, 25, 2013	<a href="#">Late Cycle PreMtg</a> Aug. 20, 2013 [Tues.]
Send Briefing Packages to Piramal	Sept. 4, 2013	By Aug. 30, 2013 [Fri.]
Issue DR Letters	Sept. 1, 2013 [Fri.]	
Late Cycle Meeting	Sept. 12, 2013	<a href="#">LateCycle Meeting</a> Sept. 10, 2013[Tues.]
Wrap Up Meeting	Nov. 3, 2013	Oct. 29, 2013 [Tues.]
OSI Clinical Inspection Summary Review	Aug. 31, 2013	
Facility Inspections	Aug. 24, 2013	
OSE Review	Aug. 23, 2013 [Fri.]	
Primary Review due to TL	Aug. 23, 2013 [Fri.]	
Secondary Review due to CDTL	Aug. 30, 2013 [Fri.]	
DRISK Review/Memo	Sept. 3, 2013[Tue.]	
CDTL Review due to DD	Nov. 8, 2013 [Fri.]	
<b>Division Director Review</b>	<b>Feb, 28, 2014 [Fri.]</b>	
<b>Month 12 Goal Date Standard, Office Sign-off</b>	<b>March 21, 2014 [Fri.]</b>	

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

/s/  
-----

SHARON P THOMAS  
12/03/2013

**From:** Thomas, Sharon  
**Sent:** Wednesday, November 27, 2013 12:54 PM  
**To:** Kevin Hennegan (khennegan@cbrintl.com); Jeanne Novak (jnovak@cbrintl.com)  
**Subject:** NDA 204677/ Florbetaben/ Statistical Information Request

NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak,

Regarding your New Drug Application (NDA 204677) for florbetaben, we have the following statistical comments/information requests:

1. Please provide data for the 82 patients together in one xlsx file (also in xpt file). The content should be the same as the attached file with additional column (an indicator variable) to identify the 31 patient group, the 23 (54-31) patient group, the 28 (82-54) patient group, and the 10 healthy volunteer group. A define file should be provided. The subject id (patient id) should be unique so that the data can be merged with other data sets in this new submission.

Please provide a response by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, Monday, December 2, 2013 and follow-up with a formal amendment submission to the NDA.

Best regards,  
*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products  
FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
11/27/2013

## MEMORANDUM OF TELECONFERENCE

**Meeting Date and Time:** November 19, 2013, 12:00 pm EST  
**Application Number:** NDA 204677

**Product Name:** Neuraceq (florbetaben) injection  
**Indication:** Detection of beta amyloid in the brain

**Sponsor's Name:** Piramal Imaging, SA (CBR International Corp-U.S. Agent)  
**Subject:** Specifications for impurities [REDACTED] (b) (4)

### FDA Participants

#### Division of Medical Imaging Products (DMIP)

Libero Marzella, MD, PhD, Director (acting)  
Alex Gorovets, MD, Clinical Team Leader, DMIP  
Eldon Leutzinger, PhD, CMC Lead, ONDQA  
Anne Marie Russell, PhD, CMC Reviewer, ONDQA  
Danae Christodoulou; PhD, Branch Chief Acting, ONDQA  
Sharon Thomas, BSc, Sr., Regulatory Project Manager, DMIP

### Sponsor/Applicant Participants

Jeanne Novak, PhD, CBR International Corp, Authorized Regulatory Representative  
Dana Weinberger, CBR International  
Kevin Hennegan, MA, Senior Director of Clinical Affairs, CBR International  
Kelly Bechter, Regulatory Associate, CBR International  
Andrew Stephens, MD, PhD, Piramal Imaging, Clinical  
Matthias Friebe, PhD VP, Radiochemistry Research, Global Drug Discovery, Piramal Imaging  
Christian Schmidt, PhD, Head CMC Operations, Piramal Imaging  
Jürgen Hirschfeld, PhD, Senior Director Regulatory Affairs, Piramal Imaging  
Mathias Berndt, Piramal Imaging

### BACKGROUND:

On August 21, 2013, FDA issued a CMC Information Request regarding the acceptance criteria for impurities [REDACTED] (b) (4) proposed specifications (IR#2, Comment #1). Subsequent communications were unable to resolve the issue (response from Piramal received September 2, 2013, followed by additional Information Request (IR#4) from FDA issued November 08, 2013 and further response from Piramal - initially a partial response by email on November 14, 2013

and a formal full response on November 18, 2013). On November 12, 2013, FDA proposed a teleconference to clarify comments from the Information Request.

The discussion items from the teleconference are indicated in ***bold italics*** below.

## **DISCUSSION:**

***FDA contacted the sponsor to discuss the CMC issue (Comment #1) regarding the proposed specifications for impurities (b) (4)***

- 1. FDA began the teleconference by advising Piramal that their response to Comment #1 from IR#2, and follow-on Comment #1 in IR #4, remains unacceptable because their proposed (b) (4) impurity specification acceptance criteria exceed the acceptable limits per ICH guidance for drug substance (ICH Q3A).***

***FDA stated the (b) (4) is treated to the same level of scrutiny as a drug substance, and as such is subject to the applicable ICH guidelines for impurities - identified impurities would need to be limited to 0.15% (or else qualified) and unspecified impurities limited to 0.10% (or else identified).***

***Piramal acknowledged that they now understood that the (b) (4) impurity specifications are subject to ICH Q3A.***

- 2. FDA asked if impurities which exceeded the qualification limit had been qualified. Piramal answered that they would check with the (b) (4) manufacturer (b) (4) and get back to the FDA.***
- 3. Piramal asked the FDA to clarify if “any unspecified impurity” should be limited to 0.10% (identification limit per ICH Q3A) or limited to 0.15% as stated in the CMC Information Request #4. FDA clarified that 0.15% was a typographical error and advised that the ICH limit of 0.10% applied to “any unspecified impurity” since the impurities were not identified. Piramal acknowledged the clarification.***
- 4. Piramal inquired if the Decision Tree in Attachment 3 in ICH Q3A could be used to justify impurity levels higher than the ICH Q3A limits. For example, to estimate absolute levels of exposure to the impurities exceeding ICHQ3A and justify their safety. FDA replied that Piramal should submit a justification based on their rationale for review as soon as possible. The acceptability of the proposal will be a review issue including Toxicology evaluation for the safety evaluation of the exposure to absolute levels of impurities.***
- 5. FDA stated that their batch history for (b) (4) lots (3 clinical and 3 commercial) was very limited and inquired if data from additional batches were available. Piramal replied that no additional batches, beyond those submitted, had been manufactured.***

6. *Piramal asked if FDA had feedback on the response submitted late the previous day (November 18, 2013). FDA explained that preliminary review of the response to the (b) (4) impurity acceptance criteria issue indicated that 4 of 7 specified impurity acceptance criteria still exceed the ICH qualification limit (see discussion above) but that the three which met the limit of 0.15% were acceptable. FDA also advised that the proposed criteria for “any unspecified impurity” exceeded the ICH identification limit (see above discussion) and that the acceptability of the total impurities acceptance criteria (2%) was contingent on the entire impurity profile of the (b) (4) (which was not yet final) but was preliminarily acceptable. FDA said they had no additional comments for the remainder of the response at this time.*
7. *FDA asked Piramal to provide a timeline for their response. Piramal said they will submit a response within this week (by November 22, 2013). The teleconference ended at 12:45 pm.*

FDA comments from Information Request #4 are formatted in bold text immediately followed by Piramal's written response, received November 18, 2013, in normal text. Note that Comment #1 is a follow-up response to the original CMC comment in Information Request #2 (issued August 21, 2013).

**FDA COMMENTS AND SPONSOR'S RESPONSE**

- The batch data and justification submitted do not support the proposed acceptance criteria of the (b) (4) (b) (4) impurities.**

**The batch data submitted include release impurity levels for three production lots (BXR5GFK, BXR5GFJ, and BXR5GLUR) and for three development lots used to manufacture the product used in clinical trials (frozen retains age 24- 45 month lots BXR4DOC, BXR4DOD, and BXR4DOE). The impurity data also include stability data to 18 months for one of these production lots (BXR5GFK) and at 18 months for the three development lots.**

**Analysis of the submitted lot history data (see Table 1 below) indicate that the proposed acceptance criteria significantly exceed the maximum levels observed in batch history. Reduce the acceptance criteria to reflect the lot history and to not exceed (b) (4) except as supported by batch history (e.g. (b) (4) (b) (4)). Any unspecified impurity should be no greater than 0.15% and the sum of all impurities should not exceed (b) (4). Submit revised specifications for the (b) (4).**

Table 1 (b) (4) Impurity Data Submitted			
Impurity	Reported levels for 6 batches: (min – max)		Proposed acceptance criteria
	At release	At 18 mos stability	
(b) (4)			

n.d.- not detectable

With the exception of the specification for “Any unspecified impurity”, the (b) (4) specifications have been revised as requested. Please refer to the updated CTD sections S.4.1.01 and S.4.5.01, and to Table 2 below.

Table 2			
Revised (b)(4) Impurity Specifications			
Impurity	Reported levels for 6 batches: (min – max)		Revised acceptance criteria
	At release	At 18 mos stability	
			(b)(4)

As shown in Table 3 the batch history for the florbetaben (b)(4) supports a higher limit for “Any unspecified impurity” than that proposed by the Agency in their written comments.

Table 3						
(b)(4) batch history: Any unspecified impurity						
Test	Batch no.	Batch no.	Batch no.	Batch no.	Batch no.	Batch no.
	BXR4D0C	BXR4D0D	BXR4D0E	BXR5GFJ	BXR5GFK	BXR5GLU
Any unspecified impurity	(b)(4)					
Mean ± SD	(b)(4)					
Use of batch	clinical trials			commercial product		

(b)(4)						
--------	--	--	--	--	--	--

Further, as discussed in Seq 0020, submitted 17 Sep 2013, the limit of (b)(4) for any unspecified impurity (and even the limit of (b)(4) for (b)(4) (b)(4) would result in an exposure level, even under worst case assumptions, that is at least (b)(4) than the ICH M7 limit for proven mutagenic substances daily administered for 10 years and beyond (b)(4). This is considered to be a reduction to a “safe

for 10 years and beyond (b) (4). This is considered to be a reduction to a “safe level”, as recommended by ICH Q3A, Attachment 3, “Decision Tree for Identification and Qualification” for unspecified impurities that are present above the identification threshold of 0.10%.

Therefore, the Sponsor considers a limit of (b) (4) for this parameter to be justified.

**2. Specifications include three columns: attribute, analytical method and acceptance criteria. For each attribute listed, specifications identify the test method used for analysis and list the acceptance criteria for the test result.**

**The submitted specifications for (b) (4) and drug product are missing analytical method for all attributes. This information needs to be added to the specifications.**

**Analytical methods submitted in the NDA are the regulatory method of record. As such, they are provided to contract laboratories/manufacturers with some type of identification which ties back to the NDA and the individual method procedure. This identification is included in the NDA specification listing of the analytical method.**

**For standard/compendial methods, (b) (4) the identification can be the USP method number. For analytical methods which are unique to the application, such as HPLC for assay/identity/impurities or GC for residual solvents, the identification is often a procedure number or analytical method number.**

**We note that the header of the (b) (4) specification document identifies test procedure S.4.2.01-01, which is the eCTD section of the NDA which holds the analytical procedures. Since this section contains all the test methods, it will not suffice to identify the individual analytical method for a specific attribute in the specification, as needed.**

**Submit revised specifications for (b) (4) and drug product which include a third column identifying the analytical method used to test the attribute.**

The (b) (4) specification (S.4.1.01) has been revised. However, we cannot provide a procedure number or analytical method number as suggested by the Agency. (b) (4)

(b) (4)  
To address the Agency’s concern regarding the identification of the individual analytical methods for specific attributes of florbetaben, the analytical methods document, CTD section S.4.2.01, was revised by dividing the document into appropriate sub-sections and providing reference to the sub-sections within the specifications document (S.4.1.01).

The drug product specifications were also revised as requested. Please refer to the updated CTD sections P.5.2.01 and P.5.2.02. In addition, a revised version of section

P.5.6.01 is provided reflecting the changes in the specifications implemented in response to FDA CMC information request 2 (dated 21 Aug 2013).

**Additional Comments**

- 3. Provide the USAN name for florbetaben. Indicate the status (accepted, pending, etc).**

The USAN name for florbetaben is FLORBETABEN F18. This name was accepted by the USAN Council on 27-Feb-2013.

- 4. Provide the LOD and LOQ values for impurities reported as n.d. (not detectable) in the submitted batch data tables for the six (b)(4) lots.**

The LOD and LOQ values as provided in CTD section S.4.3.01 for impurities are listed in Table 3.

Table 3		
LOD/ LOQ for (b)(4) Impurities		
Impurity	LOD*	LOQ
(b)(4)		

\*n.d. corresponds to < LOD

- 5. Advise if the drug product is iso-osmotic.**

The osmolality of the drug product approximately (b)(4) mOsmol/ kg. Therefore, the drug product (b)(4) To prevent potential local irritation the drug product is administered in a slow bolus injection (1 mL/6 sec) into a large vein in the arm.

- 6. Describe what happens to the (b)(4) after use.**

(b)(4)

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

/s/  
-----

SHARON P THOMAS  
11/21/2013

**From:** Thomas, Sharon  
**Sent:** Friday, November 15, 2013 5:05 PM  
**To:** Jeanne Novak (jnovak@cbrintl.com); Kevin Hennegan (khennegan@cbrintl.com)  
**Cc:** Dana Weinberger (dweinberger@cbrintl.com)  
**Subject:** FW: NDA 204677- Neuraceq (florbetaben) Chemistry Information Request

Hi Jeanne,

We would like to discuss the two Chemistry items in greater detail in Tuesday's teleconference. The CMC team will review your submission received via email on November 13, 2013, proposing (b) (4) acceptance criteria for any other impurity (b) (4), which exceeds the ICH identification limit of 0.10% per Q3A.

Also, please also note that your response to Comment #1 was partial. Please provide a full response before an assessment can be made. It would be helpful to have the full response to Comment #1 prior to the tcon – latest by Monday COB.

Below are the teleconference details.

**Tues., November 19th 12:00 pm -12:30 pm EST**

**US: / 866-692-4541**

**Germany:/ 0800-664-4253 (Toll Free )**

**Participant Passcode/ (b) (4)**

Please don't hesitate to contact me if you have any questions.

Best regards,  
*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products  
FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
11/20/2013

**From:** Thomas, Sharon  
**Sent:** Friday, November 08, 2013 3:15 PM  
**To:** Kevin Hennegan (khennegan@cbrintl.com); Jeanne Novak (jnovak@cbrintl.com)  
**Subject:** NDA 204677- Neuraceq (florbetaben) Chemistry Information Request

NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak,

Please refer to your New Drug Application (NDA 204677) for florbetaben, dated and received on December 21, 2012. We also reference your September 18, 2013 response to the Chemistry information requests dated August 21 and 23, 2013, we have the following comments:

### Chemistry

#### FDA Reply to Piramal's response to IR#2:

##### Comment #1

The batch data and justification submitted do not support the proposed acceptance criteria of the (b)(4) impurities.

The batch data submitted include release impurity levels for three production lots (BXR5GFK, BXR5GFJ, and BXR5GLUR) and for three development lots used to manufacture the product used in clinical trials (frozen retains age 24- 45 month lots BXR4DOC, BXR4DOD, and BXR4DOE). The impurity data also include stability data to 18 months for one of these production lots (BXR5GFK) and at 18 months for the three development lots.

Analysis of the submitted lot history data (see Table 1 below) indicate that the proposed acceptance criteria significantly exceed the maximum levels observed in batch history.

Impurity	Reported levels for 6 batches: (min – max)		Proposed acceptance criteria
	At release	At 18 mos stability	

n.d. not detectable

Reduce the acceptance criteria to reflect the lot history and to not exceed (b) (4) except as supported by batch history (e.g. (b) (4) (b) (4)). Any unspecified impurity should be no greater than (b) (4) and the sum of all impurities should not exceed (b) (4). Submit revised specifications (b) (4).

Comment #3:

Specifications include three columns: attribute, analytical method and acceptance criteria. For each attribute listed, specifications identify the test method used for analysis and list the acceptance criteria for the test result.

The submitted specifications for (b) (4) and drug product are missing analytical method for all attributes. This information needs to be added to the specifications.

Analytical methods submitted in the NDA are the regulatory method of record. As such, they are provided to contract laboratories/manufacturers with some type of identification which ties back to the NDA and the individual method procedure. This identification is included in the NDA specification listing of the analytical method.

For standard/compendial methods, (b) (4), the identification can be the USP method number. For analytical methods which are unique to the application, such as HPLC for assay/identity/impurities or GC for residual solvents, the identification is often a procedure number or analytical method number.

We note that the header of the (b) (4) specification document identifies test procedure S.4.2.01-01, which is the eCTD section of the NDA which holds the analytical procedures. Since this section contains all the test methods, it will not suffice to identify the individual analytical method for a specific attribute in the specification, as needed.

Submit revised specifications for (b) (4) and drug product which include a third column identifying the analytical method used to test the attribute.

Additional Comments:

1. Provide the USAN name for florbetaben. Indicate the status (accepted, pending, etc).
2. Provide the LOD and LOQ values for impurities reported as n.d. (not detectable) in the submitted batch data tables for the six (b) (4) lots.

3. Advise if the drug product is iso-osmotic.
4. Describe what happens to the [REDACTED] <sup>(b) (4)</sup> after use.

Please provide a response by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, Friday, November 15, 2013 and follow-up with a formal amendment submission to the NDA.

Best regards,  
*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products  
FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
11/08/2013

**PeRC PREA Subcommittee Meeting Minutes  
July 10, 2013**

**PeRC Members Attending:**

Peter Starke  
Tom Smith  
Robert “Skip” Nelson  
William J. Rodriguez  
Wiley Chambers (did not review saxagliptin/metformin WR)  
Lily Mulugeta  
Daiva Shetty  
Gregory Reaman  
Kevin Krudys  
Ruthanna Davi  
Jane Inglese  
George Greeley  
Rosemary Addy  
Maura O’Leary  
Andrew Mosholder  
Melissa Tassinari  
Shrikant Pagay  
Diane Murphy  
Susan McCune  
Rachel Witten

**Guests Attending:**

Dionna Green (OCP)	Sang Chung (OCP)
Erica Radden (PMHS)	Raymond Chiang (DMEP)
Courtney Suggs (OCP)	Le Ping Pian (DB2)
Gilbert Burckart (OCP)	Frank Pucino (DMEP)
Donna Snyder (PMHS)	Mark Rothmann (DB2)
Terrie Crescenzi (OPT)	Kevin Watt (OPT)
GT Wharton (OPT)	Jeffry Florian (OCP)
Allyson Karesh (PMHS)	Katherine Schumann (OCP)
Renan Bonnel (OPT)	Linda Lewis (DAVP)
Fred Alavi (DMEP)	Mary Singer (DAVP)
William Chong (DMEP)	Sofia Chaudhry (DPARP)
Karen Mahoney (DMEP)	Susan Limb (DPARP)
Lokesh Jain (OCP)	Ping Ji (OCP)
Satjit Brar (OCP)	Jennifer Pippins (DPARP)
Colette Jackson (DPARP)	

**Agenda**

(b) (4)

NDA 204-677 Neuraceq (florbetaben F18) Full Waiver

(b) (4)

(b) (4)

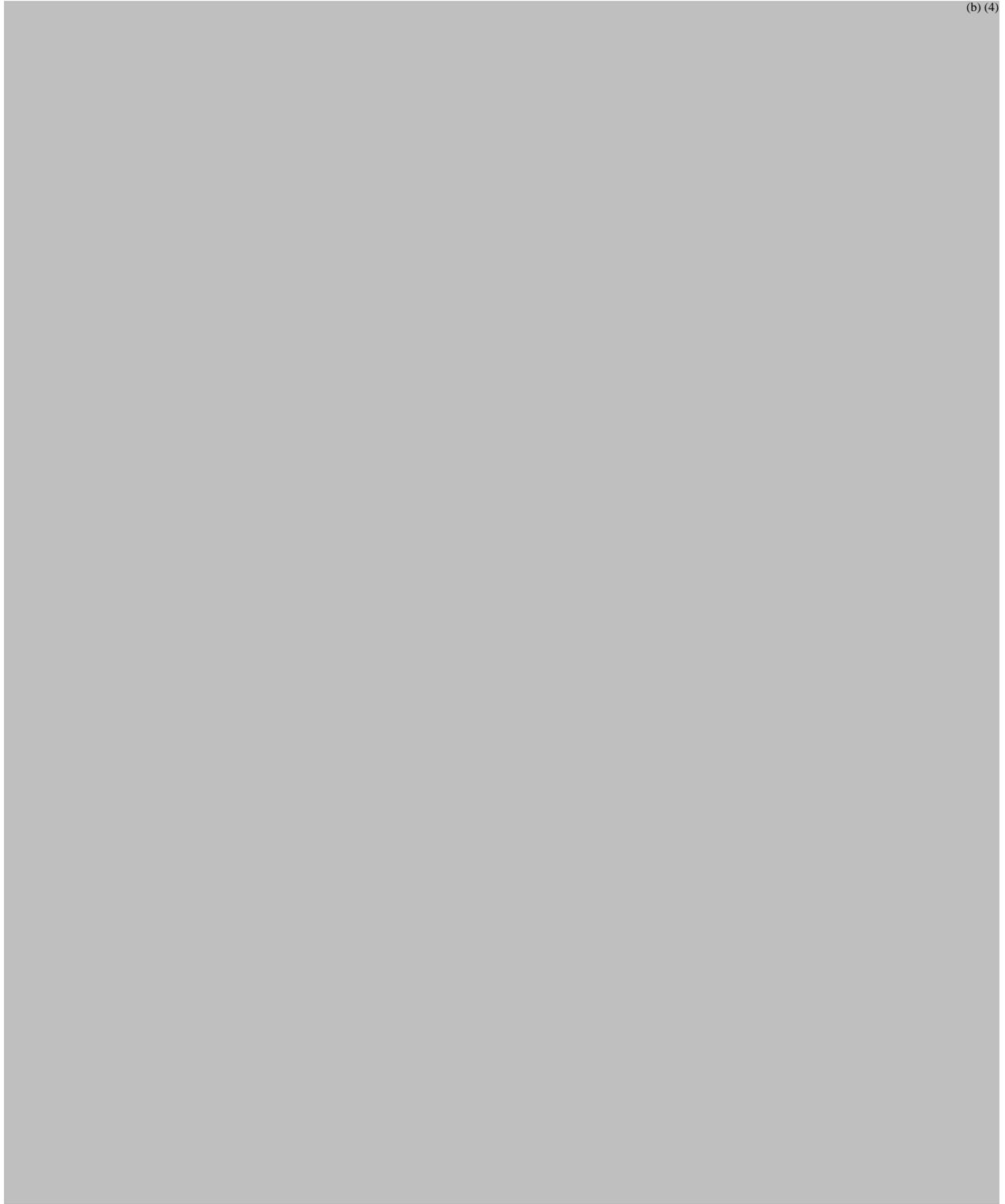
**Neuraceq Full Waiver**

- NDA 204-677, Neuraceq (florbetaben F18), was studied 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.
- The application was submitted on December 21, 2012 and has a PDUFA date of December 21, 2013.
- This application triggers PREA as a new: indication, active ingredient, route of administration, dosing regimen and dosage form.
- The Division believes a full waiver is appropriate because studies are impossible or highly impracticable because the disease/condition does not exist in children.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impracticable because the disease/condition does not exist in children.

(b) (4)





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

/s/  
-----

JANE E INGLESE  
10/28/2013

**From:** Thomas, Sharon  
**Sent:** Wednesday, October 23, 2013 12:56 PM  
**To:** 'Kevin Hennegan'  
**Cc:** Jeanne Novak; Dana Weinberger  
**Subject:** RE: NDA 204677 - Follow up regarding agency response to 20 September clinical submission/ Information Requests

Dear Kevin,

Regarding Piramal's response to the substantive clinical issues, received via email on September 20, 2013, the submission is currently under review. Please see the information requests/comments below regarding your upcoming submission in November:

**\*\*\*In reference to the new read study being conducted on images from the 82 patients with histopathology standard of truth, if you plan to submit new data analyses, we request that you include in your submission the entire data in .xpt format (with define.pdf file) for 82 patients consisting of indicator variable (1 for first 31 patients (study 14595), 2 for additional 23 patients (study 16034), 3 for the remaining patients (The new study), total is 31+23+28=82), SOT (using BSS neuritic plaques), baseline diagnostic condition, all demographic variables, PET classification (positive or negative) according to the 5 new web-based trained readers.**

Please don't hesitate to contact me if you have any questions.

Best regards,  
Sharon

Sharon Thomas, RPM  
Division of Medical Imaging Products  
ODE IV/ CDER / FDA  
(301) 796-1994 (office)

**From:** Kevin Hennegan [<mailto:khennegan@cbrintl.com>]  
**Sent:** Wednesday, October 23, 2013 12:48 AM  
**To:** Thomas, Sharon  
**Cc:** Jeanne Novak; Dana Weinberger  
**Subject:** NDA 204677 - Follow up regarding agency response to 20 September clinical submission

Dear Sharon,

I am writing to follow up regarding Piramal Imaging's response to the substantive clinical issues, sent via email on 20 September 2013 (NDA sequence 0024). Can you give us any update on the timeline for when we might receive feedback from the reviewers on this submission?

Thank you!

Kevin

Kevin Hennegan, MA  
*Senior Director of Clinical Affairs*  
CBR International Corp. ®  
720-746-1190  
720-746-1192 (Fax)  
[www.cbrintl.com](http://www.cbrintl.com)

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

/s/  
-----

SHARON P THOMAS  
10/23/2013



IND 78868

**GENERAL ADVICE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your Investigational New Drug Application (IND) 78868, submission dated October 1, 2013 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (florbetaben F 18) Injection.

We also refer to your clinical study protocol FBB-0101-13 titled: "A non-interventional study to assess the efficacy, reliability, and reproducibility of the FBB  $\beta$ -amyloid PET scan visual assessment method as trained via an electronic training tool, using images from the histopathology study 14595." We have the following comments and recommendations:

1. The study is not fully adequate in design and the analysis plan is not sufficiently conservative in approach to provide the evidence necessary to establish the efficacy of florbetaben F 18. The inferences that can be drawn from a study based on the reinterpretation of images are somewhat limited.
2. The thresholds you have proposed to demonstrate the ability of florbetaben F 18 to detect beta amyloid in the brain are marginal (lower limit of the 95% confidence intervals  $> 0.5$  for specificity and  $> 0.6$  for sensitivity) and are not adequately justified clinically or statistically. The performance might raise concerns about the strength of the evidence for the clinical usefulness of a florbetaben F 18 scan.
3. We note that study protocol lacks detailed information on the reader training and image interpretation procedures.
4. We recommend the following revisions to the study's primary efficacy analysis.
  - a. Include only patients with histopathologic diagnosis. Subjects who lack a truth standard are not appropriate for the assessment of sensitivity and specificity.
  - b. Pre-specify the truth standard as the histopathology assessment of neuritic beta-amyloid plaque using Bielschowsky silver staining according to CERAD criteria.

- c. Include in the primary analysis patients with uninterpretable or missing images by one or more readers. Impute a reader's missing image interpretation as a diagnostic failure (worst case).
- d. Specify that for the study to succeed the combined hypotheses need to be rejected in the same 3 readers.

If you have any questions, please feel free to contact Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994 or via email at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

LIBERO L MARZELLA  
10/18/2013



NDA 204677

**GENERAL ADVICE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to your response to the FDA's statistical substantive review issues, received September 18, 2013 via email, the teleconference held on September 23, 2013, and your submission on September 27, 2013 titled "Response to FDA request for Information Request Received: 23 September 2013".

We have the following comments/recommendations:

1. Provide the information to obtain the subject-level SOT used in Study 16034 from the original data source for all 54 subjects (with evaluable brains) (similar table like Table 1 in the response to FDA statistical information request seq. No. 0023). There are 32 subjects (31 evaluable as you mentioned) in the data disy01 (pathology data from 14595), Please clarify how do you use d-basic.sas to obtain the brain-level SOT for the additional 23 subjects (brains).
2. Recommend using ADAM and SDTM data standard for future submissions.
3. There are only 32 subjects in the excel file. Do you have similar file for all the 54 subjects (including additional 23 brains)?

You will receive clinical team's Information Request at a later date.

If you have any questions, please feel free to contact Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994 or via email at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

LIBERO L MARZELLA  
10/10/2013

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date/Time:** Monday, September 23, 2013 at 3:45 PM- 4:45 PM  
**Meeting Location:** White Oak, Bldg. 22, Conf. Room 5266

**Application Number:** NDA 204677  
**Product Name:** Neuraceq (Florbetaben F 18) Injection  
**Sponsor/Applicant Name:** Piramal Imaging SA (c/o CBR International- US Agent)

**Subject:** Statistical substantive review issues

### FDA Participants:

Division of Medical Imaging Products (DMIP)  
Liberio Marzella, M.D., Ph.D., Acting Division Director, DMIP  
Alexander Gorovets, M.D., Deputy Director, DMIP  
Brenda Ye, M.D., Medical Officer, DMIP  
Lan Huang, Ph.D., Statistical Reviewer, DBV  
Jyoti Zalkikar, Ph.D., Statistical Supervisor, DBV  
Sharon Thomas, Sr. Regulatory Health Project Manager, DMIP

### Sponsor/Applicant Participants:

Piramal Imaging SA  
Kelly Bechter, Regulatory Associate, CBR International

(b) (4)

Kevin Hennegan, MA, Senior Director of Clinical Affairs, CBR International  
Jürgen Hirschfeld, Ph.D., Senior Director Regulatory Affairs, Piramal Imaging  
Norman Koglin, Ph.D., Director Portfolio Management, Piramal Imaging  
Andre Mueller, Ph.D., Director Radiopharmacology, Piramal Imaging  
Jeanne M. Novak, Ph.D., Authorized FDA Representative and US Agent, CBR International  
Andrew Stephens, MD, Ph.D., VP Clinical Research and Development, Piramal Imaging  
Dana Weinberger, Ph.D., Director of Regulatory Affairs, CBR International

### 1.0 BACKGROUND:

On August 29, 2013, FDA submitted a Late-Cycle Meeting Background Package to Piramal that contained substantive statistical review issues to date in preparation for the Late-Cycle review meeting held September 10, 2013. Piramal responded via email on September 18, 2013 with a submission to address the statistical deficiencies. In addition, Piramal requested an informal teleconference to obtain clarification and further discuss the statistical items. On September 19, 2013, FDA agreed to proceed with the teleconference. The discussion points are shown in ***bold italics*** below.

## **2.0 DISCUSSION:**

- 1. FDA asked the sponsor to provide information on the subject-level Standard of Truth used in Study 16034 from the original data source. In addition, the FDA requested the raw data instead of derived data for studies 14595 and 16034.*
- 2. FDA recommended tables in a narrative report with column headings, definitions, explanation of the abbreviations, and links to the datasets.*
- 3. FDA requested a data listings for each patient, brain region, amount of amyloid established in each region. The sponsor to include another column that flags positive/negative for amyloid.*
- 4. FDA commented that CSR appendix 16.2.6 for both studies (14595 and 16034) requires additional definitions and is difficult to read in its current format. FDA proposed the new data standard- ADAM and SDTM for future submissions.*
- 5. FDA asked the sponsor to clarify the non-evaluable brain out of the 32 brains.*

## **3.0 ACTION ITEMS:**

- Piramal agreed to provide a formal submission to address the items above.

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

/s/  
-----

SHARON P THOMAS  
10/08/2013

**From:** Thomas, Sharon  
**Sent:** Monday, August 26, 2013 4:28 PM  
**To:** 'Kevin Hennegan'; Jeanne Novak; Dana Weinberger  
**Subject:** NDA 204677 /Florbetaben/ Labeling

Dear Kevin,

We have the following labeling recommendations at this time for florbetaben:

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 USP controlled room temperature 25°C (77°F); excursions permitted to (b) (4).

2. Vial Labels:

- a) Delete the (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.

3. Shield Labeling:

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

If you have any questions, please don't hesitate to contact me.

Best regards,

*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products

FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
08/26/2013

**From:** Thomas, Sharon  
**Sent:** Friday, August 23, 2013 4:18 PM  
**To:** 'Kevin Hennegan'; Jeanne Novak; Dana Weinberger  
**Subject:** NDA 204677 /Florbetaben/ CMC Information Request #2

NDA 204677

**INFORMATION REQUEST #2**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak,

Please refer to your New Drug Application (NDA 204677) for florbetaben, dated and received on December 21, 2012. We are reviewing the Chemistry section of your submission and have additional comments and information requests:

1.  (b) (4)
2. Revise the drug product specifications  (b) (4)
3. Provide executed batch record(s) for the drug product.

Please provide a response by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by 12:00 pm, Friday, September 6, 2013 and follow-up with a formal amendment submission to the NDA. If you have any questions, please don't hesitate to contact me.

Best regards,  
*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products  
FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
08/23/2013

**From:** Thomas, Sharon  
**Sent:** Wednesday, August 21, 2013 4:10 PM  
**To:** 'Kevin Hennegan'  
**Cc:** Jeanne Novak; Dana Weinberger  
**Subject:** NDA 204677 /Florbetaben/ CMC Information Request

NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak,

Please refer to your New Drug Application (NDA 204677) for florbetaben, dated and received on December 21, 2012. We are reviewing the Chemistry section of your submission and have the following comments and information requests:

1. The justification for (b) (4) impurity acceptance criteria proposed in the (b) (4) specifications is not acceptable because the clinical batch history submitted for (b) (4) impurities is not batch release data (b) (4) but rather test results of retains tested at lot age (b) (4).
  - Provide clinical batch release data for impurities (b) (4) conducted using the NDA analytical method (Procedure S.4.2.01) or equivalent to support the proposed justification.
  - If that data are not available, provide a justification for the suitability of submitted data from tests conducted on retains. Include a complete description of the storage history of the sample tested - age of lot when retain was taken, age of lot at time of test, duration of retain period prior to test, storage conditions prior to retain (b) (4) storage conditions during retain period and storage conditions after retain prior to test.
  - When a suitable lot history is established for the basis of justification, revise the (b) (4) acceptance criteria for impurities to reflect lot history. The current criteria exceed proposed lot history by a substantial amount.
2. The (b) (4) stability data submitted on three clinical lots and one production lot are not sufficient to support the proposed (b) (4) retest period. A minimum of 18 month long-term data on three lots are needed to support the proposed retest period.
  - Provide long term stability data collected on three lots of (b) (4) at age 0,3,6,9,12 and 18 months using the NDA analytical methods for the attributes proposed. Data collected on retain samples may be supportive, but are not suitable as primary stability data.
  - If that data are not available, propose a retest period supported by available data.

3. Revise specifications to include the analytical procedure/method number for each test/attribute, including the (b) (4) and drug product specifications.
4. The proposed acceptance criteria for the following attributes in the drug product specifications are not supported by the submitted clinical and commercial drug product lot release data – pH, (b) (4), any other unspecified impurities and sum of unspecified impurities. Reduce the acceptance criteria to reflect lot history. Alternately, provide clinical lot release data to support the proposed acceptance criteria. Include a summary of lot history (minimum, maximum, median, mean values) for each attribute according to category defined by the formulation and generation of manufacturing process (e.g. Phase II/III formulation with 3rd generation manufacturing process). Of particular interest is a summary for lots used in the pivotal efficacy study #14595 (n~229).

Please provide a response by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, Wednesday, September 4, 2013 and follow-up with a formal amendment submission to the NDA.

Best regards,

*Sharon*

.....  
Sharon Thomas  
Senior Regulatory Project Manager  
Division of Medical Imaging Products  
FDA/CDER/ODEIV  
(301)796-1994  
[Sharon.thomas@fda.hhs.gov](mailto:Sharon.thomas@fda.hhs.gov)

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

/s/  
-----

SHARON P THOMAS  
08/21/2013



NDA 204677

**GENERAL ADVICE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to your email communication, dated July 31, 2013, containing a request for a submission of information regarding [REDACTED] (b) (4) to NDA 204677.

We have the following comments/recommendations:

1. We do not agree to the proposed amendment to add [REDACTED] (b) (4) during the review of the NDA. Nor do we agree with use of [REDACTED] (b) (4)

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Eric Duffy, Ph.D.  
Division Director  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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

/s/  
-----

ERIC P DUFFY  
08/12/2013

**From:** Thomas, Sharon  
**Sent:** Tuesday, July 30, 2013 4:06 PM  
**To:** 'Kevin Hennegan'  
**Cc:** 'Jeanne Novak'; 'Dana Weinberger'  
**Subject:** NDA 204677, Florbetaben, AC Meeting Request/ Stats IR

Dear Mr. Hennegan:

Reference is made to NDA 204677 and your request for an AC meeting (email communication dated July 23, 2013). Please see the Division's response in the attached Advice letter.



NDA  
77General Advice Le

We also have the following request for information from the statistical reviewer:

- **Provide the unique patient id, gender, sex, age at baseline, baseline clinical diagnosis for subjects in A42404 (Study 123456) and Study 311722. The data should be in xpt format.**

Please submit a response via email on Thursday, August 1st by 12:00 pm (EDT) and follow-up with a formal NDA amendment submission.

If you have any questions, please don't hesitate to contact me.

Best regards,  
Sharon

~~~~~

Sharon Thomas  
Senior Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Office of New Drugs/ CDER/ FDA  
10903 New Hampshire Avenue,  
Building 22, Room 5231  
Silver Spring, MD 20993  
(301) 796-1994 (office)  
(301) 595-7922 (fax)

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

/s/  
-----

SHARON P THOMAS  
07/30/2013



NDA 204677

**GENERAL ADVICE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to your email communication, dated July 23, 2013, containing a request for an Advisory Committee (AC) meeting. We have the following comments/recommendations:

- We appreciate your suggestion and refer you to our June 14, 2013 Mid-Cycle Communication in which we stated that an Advisory Committee meeting would not be necessary for the completion of our NDA review. In that communication, we highlighted our concerns with the development of the reading methodology and the imaging performance characteristics of florbetaben. Since our review of your application is currently ongoing, we will re-assess the need for an AC meeting after further review of the NDA. We will discuss with you the status of our review and any substantive deficiencies identified at the Late-Cycle meeting scheduled for September 10, 2013. We appreciate the scientific complexities, but don't have any requests for additional scientific information at this time.

If you have any questions, please feel free to contact Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994 or via email at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

LIBERO L MARZELLA  
07/25/2013

---

**From:** Thomas, Sharon  
**Sent:** Monday, July 01, 2013 2:12 PM  
**To:** 'Kevin Hennegan'; 'Jeanne Novak'  
**Subject:** NDA 204677 / Florbetaben/CMC Information Request

NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act, for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq. We have the following comments and information requests:

**\*\*\*\*In the CMC amendment dated 31-May-2013, reference was made to three drug master files (DMFs) for the (b) (4) module (DMFs (b) (4)). In the submission, Letters of Authorization (LOA) from the DMF holder, (b) (4) were provided for each of these DMFs. However, these LOAs have not been submitted to the DMFs and are needed to authorize reference. Contact (b) (4) to arrange for submission of the LOAs to their DMFs.**

Please provide a response by e-mail to my attention by COB, July 12, 2013 and follow-up with a formal amendment NDA submission. If you have any questions please feel free to contact me.

Best regards,  
Sharon

Sharon Thomas, RPM  
Division of Medical Imaging Products  
(301) 796-1994 (office)

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

/s/  
-----

SHARON P THOMAS  
07/01/2013



NDA 204677

**INFORMATION REQUEST**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act, for Florbitaben (BAY 94-9172) Solution for Injection 300 MBq.

We are reviewing the Microbiology section of your submission and have the following comments and information requests.

1. Your application contains a letter of authorization (dated 05 August 2011) from (b) (4), to reference their master file for (b) (4). This letter is addressed to Bayer Healthcare Pharmaceuticals, Inc. You should request that (b) (4) submit a letter authorizing your company to reference this master file. You should also amend your application (Section 1.4.2) with this letter of authorization.

Please provide a response by e-mail to Ms. Sharon Thomas, Regulatory Project Manager at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, July 5, 2013.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, MD, PhD  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

LIBERO L MARZELLA  
06/24/2013

---

**From:** Thomas, Sharon  
**Sent:** Friday, June 21, 2013 12:21 PM  
**To:** 'Kevin Hennegan'  
**Cc:** Jeanne Novak; Dana Weinberger  
**Subject:** RE: NDA 2046677/Sponsor's Response to Clinical Information Requests and Request for Teleconference/

Dear Kevin,

Thank you for providing the Sponsor's responses to address Items 1-4 provided in the FDA's Information Request dated May 17, 2013.

The Division has decided to deny your request for an informal teleconference proposed, June 24 - July 2, 2013. The issues are currently under review and we will request additional information if needed. We believe a more substantive discussion will occur during the Late Cycle meeting and we will address each question below. Please feel free to contact me if you have additional comments/concerns.

Thank you,  
Sharon

\*\*\*\*\*

Sharon Thomas  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
ODE IV / CDER / FDA  
(301) 796-1994 (office)

**From:** Kevin Hennegan [mailto:khennegan@cbrintl.com]  
**Sent:** Tuesday, June 18, 2013 6:52 PM  
**To:** Thomas, Sharon  
**Cc:** Jeanne Novak; Dana Weinberger  
**Subject:** NDA 2046677/Sponsor's Response to Clinical Information Requests and Request for Teleconference/

Hi Sharon,

Thank you for providing the FDA's minutes. I have attached the Sponsor's response to Items 1-4 from the Agency's May 17, 2013 Information Request. This response will be formally submitted to the NDA this week.

I am sending this response via email now because, as we have previously discussed, Piramal would like to request an informal teleconference with Dr. Gorovets, and other members of the clinical review team who might be appropriate, to discuss specific questions. Would it be possible to schedule this teleconference sometime between June 24 and July 2, 2013? As many of the Sponsor's participants will be in Germany for the call, a time before noon Eastern time is preferred. The specific questions for discussion are presented at the end of the response, and are also provided below.

- 1) Does the overview of clinical studies, as presented in Table 2 of the Clinical Response, provide the information requested during the Mid-cycle Communication Meeting?
- 2) Does the FDA agree that our visual assessment method as used by in-person trained readers in study 14595 fulfills clinically appropriate criteria for both sensitivity and specificity?
- 3) Does the FDA agree that our current electronic training tool performs adequately in the intended use population?
- 4) Does the FDA agree that the results of study 312043 (also confirmed in the MCI subset in study 16034) provides additional confidence that florbetaben reliably detects amyloid deposits in the brains of patients likely to undergo testing in clinical practice?
- 5) Does the FDA agree that the results of studies 14595, 16034 and 312043, when taken together, support the ability of florbetaben PET imaging to identify patients unlikely to have Alzheimer's disease?
- 6) We understand that the FDA has concerns with the onsite-histopathology. Does the FDA agree that a consensus panel histopathology assessment is an appropriate standard of truth?

Thank you for your help in scheduling this call. I will give you a call in the morning to confirm receipt of this email and follow up. Please do not hesitate to call me at (720) 746-1190 if you have any questions.

Best regards,

Kevin

Kevin Hennegan, MA  
*Senior Director of Clinical Affairs*  
CBR International Corp. ®  
720-746-1190  
720-746-1192 (Fax)

[www.cbrintl.com](http://www.cbrintl.com)

*This electronic transmission (including any and all attachments) is intended solely for the use of the individual or entity to whom it is addressed and may contain information that is privileged and/or confidential.*

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

/s/  
-----

SHARON P THOMAS  
06/21/2013



NDA 204677

**MID-CYCLE COMMUNICATION**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act, for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq.

We also refer to the face-to-face meeting between representatives of your firm and the FDA on May 21, 2013. The purpose of the Mid-cycle Communication Meeting was to provide you an update on the status of the review of your application.

A record of the meeting is enclosed for your information.

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** May 21, 2013, 2:00 pm - 3:00 pm (EDT)  
**Application Number:** NDA 204677  
**Product Name:** Neuraceq (florbetaben) injection  
**Indication:** Detection of beta amyloid in the brain  
**Sponsor's Name:** Piramal Imaging, SA (CBR International Corp-U.S. Agent)

**FDA ATTENDEES:**

Shaw Chen, MD, PhD, Deputy Director, Office of Drug Evaluation IV (ODEIV)  
Rafel Rieves, MD, Director, Division of Medical Imaging Products (DMIP)/ *Meeting Chair*  
Liberio Marzella, MD, Deputy, Division Director, DMIP  
Alex Gorovets, MD, Clinical Team Leader, DMIP  
Lucie Yang, MD, PhD, Primary Medical Team Leader, DMIP  
Brenda Ye, MD, Primary Reviewer, DMIP  
Eldon Leutzinger, PhD, CMC Team Leader, ONDQA  
Erika Pfieler, PhD, Microbiologist, OPS/NDMS  
Jyoti Zalkikar, PhD, Statistical Team Leader, DMIP  
Lan Huang, PhD, Statistical Reviewer, DMIP  
Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5  
Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5  
Ira Krefting, MD, Safety Deputy Director, DMIP  
CDR Sandra Rimmel, OSE Regulatory Project Manager  
Kevin Wright, Pharm D, DMEPA reviewer  
Joyce Weaver, PharmD, DRISK reviewer  
Sharon Thomas, BSc, Sr., Regulatory Project Manager, DMIP /*Meeting Recorder*

**SPONSOR ATTENDEES:**

Andrew Stephens, MD, PhD, Piramal Imaging, Clinical  
Jeanne Novak, PhD, CBR International Corp, Authorized Regulatory Representative  
Ana Catafau, MD, PhD, Piramal Imaging, Clinical  
Norman Koglin, PhD, Piramal Imaging, Clinical and Non-clinical  
Andre Müller, PhD, Piramal Imaging, Clinical and Non-clinical  
Kelly Bechter, CBR International Corp., Regulatory  
Jürgen Hirschfeld, PhD, Piramal Imaging, Sponsor representative, regulatory  
Kevin Hennegan, MA, CBR International Corp., Regulatory  
(b) (4)  
Matthias Friebe, PhD, Piramal Imaging, CMC



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

On April 17, 2013, FDA sent a request for information that contained Chemistry and Clinical comments and asked the sponsor to address the Clinical items during the Post-Mid-cycle Communication Meeting. On May 21, 2013, the sponsor submitted an overview of the pivotal studies (Attachment 1) and responses to FDA's comments. For the purposes of the minutes, the FDA's information requests are in regular font and the discussion points are indicated in ***bold italics*** below.

1. We are concerned about the imaging performance characteristics (particularly specificity) of your product, as defined by comparison of imaging outcomes to a truth standard. Using the PET reading methodology proposed for future clinical practice, the five blinded readers, after being trained by the training DVD, achieved a specificity of 62.5 - 91.7%, with the lower bound of 95% confidence interval (CI) being as low as 43.1%. Four of the five blinded readers failed to reject the pre-specified null hypothesis on specificity (lower bound of 95% CI of specificity  $\leq 0.7$ ). In this regard, Study 16034 failed to achieve its objectives. The specificity decreased even further (both the point estimates and lower bound of 95% CI) when the 10 healthy volunteers were excluded. Even though the study won on the primary efficacy endpoint of inter-reader agreement, the five blinded readers appear to agree on the wrong thing with regard to specificity

***Discussion Point:***

***The sponsor explained that the lower limits of the 95% confidence intervals for sensitivity and specificity were to be higher than the thresholds of 60 and 70%, for at least 3/5 readers. The sponsor agreed with FDA that the endpoint was not met, as only 1/5 readers exceeded the specificity threshold. The sponsor pointed out that data from Phase 2 Study 311741 showed better performance characteristics using clinical diagnosis as the standard of truth. FDA explained that the amyloid imaging Advisory***

***Committee meeting in 2008 had concluded that histopathology, rather than clinical diagnosis, should be the standard of truth for amyloid imaging agents, as clinical diagnosis is unreliable and an insufficient surrogate for amyloid in the brain. The sponsor further proposed that*** (b) (4)

***. FDA noted given these limitations, FDA did not provide a favorable opinion of this proposal. The sponsor may choose to submit this presentation and these additional analyses as an amendment to the NDA.***

2. Since Study 16034 assesses how the product would perform in future clinical practice, this study bears greater clinical significance than Study 14595, which did not assess performance characteristics of the product using read methods simulating future clinical practice. For example, Study 14595 used a majority read of three independent readers in the primary efficacy analysis. However in clinical practice, most PET scans will be read by one reader, rather than the majority read of three readers. In addition, all subjects in Study 14595 had brain magnetic resonance imaging (MRI), and the blinded readers had the benefit of co-registered images of PET and MRI. There is little doubt that MRI offers superior image contrast between brain gray matter and white matter than PET (alone) imaging. Distinction between brain gray and white matter is a key requirement in Florbetaben PET image interpretation. However in current clinical practice, many centers in the U.S. may not have the capacity for PET-MRI imaging. Furthermore, blinded readers in Study 14595 had in-person training with additional feedback during the training. Therefore Study 14595 appears to show the product's bioactivity in localization of amyloid, based upon brain regional sensitivity and specificity calculations performed from non-clinically applicable imaging results. This bioactivity does not appear to have translated into acceptable imaging test performance when images are interpreted using the clinically-applicable reader training method.

**Discussion Point:**

***The sponsor stated that Study 14595 used a majority read of three independent readers in the primary efficacy analysis,, but individual reader data were also collected and presented in NDA. The sponsor explained that in study 14595 the MRI scans were not used for subject-level reads. Subject-level scoring method was the same for 14595 and 16034 and a comprehensive post-approval training program will involve both electronic and in-person training, which are further being developed incorporating input from the FDA.***

***With respect to interpreting the primary endpoint of “agreement” in Study 16034, FDA stated that the secondary endpoint hypothesis testing must also support the agreement result because the readers must agree on the correct interpretations. Agreement on incorrect interpretations suggests an insufficient interpretation method.***

3. We understand that the proposed clinically-applicable PET reading methodology underwent multiple revisions during its development, and one of the early revisions appeared geared toward enhancing sensitivity, which apparently was achieved at the cost of specificity. We urge you to further refine the proposed PET reading methodology, including the training DVD, to enhance your product’s imaging test specificity while retaining acceptable sensitivity. For example, perhaps a simpler binary reading methodology (somewhat similar to that used in Study 14595) has merit. Another suggestion would be to emphasize in the training DVD the importance of correctly interpreting PET images from patients without brain amyloid deposition (the training DVD does not appear to emphasize the importance of correctly interpreting amyloid negative images). Perhaps other factors in the proposed clinically-applicable PET reading methodology could be refined to develop a robust reading methodology.

**Discussion Points:**

***FDA noted that the performance data were quite different between the regional and subject level reads. FDA proposed that there was a systematic error in the reading methodology and/or training DVD. The sponsor responded that the skewed specificity results do not indicate that there is a deficiency with their PET reading methodology or Reader Training Program. The sponsor stated that the proposed PET scoring approach is binary: ‘moderate’ (BAPL2) and ‘pronounced’ (BAPL3) are both considered as positive. BAPL 2 and BAPL 3 scores are technically useful for the nuclear medicine physician, but do not impact clinical practice. Retaining the BAPL2 level aids the reader in identifying difficult cases for more careful review. FDA further suggested that in the proposed PET reading methodology, a BAPL score of 2 could potentially become a ‘hedge’ when the reader was in fact unsure if the images should be read negative or positive. FDA suggested the sponsor to further analyze the BAPL 2 reads to try to estimate whether the BAPL option may have contributed to the insufficient specificity results. An additional suggestion from the FDA was to force the readers to first determine positive or negative and lock the results before allowing readers to further subclassify into BAPL 2 or BAPL 3.***

4. The product’s proposed labeling (Sequence 9, April 15, 2013) appears to selectively cite clinical data that do not truly reflect the product’s imaging test performance characteristics. For example, (b) (4)

**Discussion Point:**

*The sponsor stated that Onsite pathology was selected for additional post-hoc analysis. During the applicant orientation meeting, great emphasis was put on the best subject-level SoT and a whole brain SoT according to CERAD was requested. The onsite pathologists had access to clinical data, as required by CERAD guidelines, but were blinded to the results of the PET visual read. FDA restated concerns over using onsite histopathology as the standard of truth, as onsite data often lack standardization and could introduce bias.*

**3.0 INFORMATION REQUESTS**

On March 22, 2013, FDA submitted the following Microbiology Comments and requested a formal response by May 30, 2013 to the Chemistry Information Requests submitted on April 17, 2013:

**Microbiology**

- BB-MF (b) (4) is being reviewed to support a new drug application (Florbetaben, Piramal Imaging SA.) (b) (4)

Submit this information.

**Discussion Point:**

*FDA informed the sponsor of the outstanding Information Request with (b) (4) regarding the review of (b) (4).*

**Chemistry**

- Provide a table listing the doses of clinical trial product administered to patients for each generation of manufacturing process (b) (4) and formulation (development (b) (4) Include lot numbers, manufacture dates, synthesis

module used, site, trial number and other pertinent information. Discuss the effect of manufacturing process changes on the product, including analytical methods, and the comparability to planned commercial product. Highlight clinical lots submitted in Module 3.2.P.5.4.02

- Provide additional information on the proposed commercial (b) (4) (b) (4) We recommend that a Type V DMF be submitted by the (b) (4) manufacturer. Refer to *Guidance PET Drug Applications – Content and Format for NDAs and ANDAs* (August 2011) for the information to provide, which should include the following:
  - Equipment description and principle of operation
  - Equipment specifications
  - Quality system information
  - Design Controls
  - Performance standards essential requirements
  - Design verification testing including programming logic / software testing
  - Safety margin testing
  - Equipment shelf-life
  - Risk assessment including Failure Mode, Effects and Criticality Analysis (FMECA)
  - Functional and electrical testing
  - Bench testing including extraneous environment testing.
  - Data for performance verification studies
  - Results of USP extractable study per chapter <381> and USP biological reactivity as per chapter <87> and chapter <88> on elastomeric components that come in contact with the drug
- Similarly, provide a description of the (b) (4) used to manufacture the lots of clinical product for which batch data were submitted. Discuss differences compared to the commercial (b) (4) and their impact on product quality – including analytical methods.

**Discussion Point:**

*The sponsor agreed to provide a formal response to the Chemistry comments cited above by the end of May.*

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

The FDA stated that there have been no safety/risk management concerns identified in this phase of the review.

**5.0 ADVISORY COMMITTEE MEETING**

FDA stated that there are no plans for an Advisory Committee meeting to review the application.

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The FDA informed the Sponsor that the proposed Late-cycle Meeting was tentatively scheduled for Tuesday, September 10, 2013 at 2:00 PM – 3:00 PM.

**7.0 ATTACHMENTS AND HANDOUTS:**

Piramal's slides (May 21, 2013) to FDA's responses and comments.

29 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

LIBERO L MARZELLA  
06/14/2013

## TELECON MINUTES

**TELECON DATE:** 05/31/13 **TIME:** 4:00 PM

**NDA:** 204677

**DRUG:** Florbetaben

**TYPE of TELECON:** Guidance

**FDA PARTICIPANTS:**

Division of Medical Imaging Products (DMIP)

Alex Gorovets, MD, Clinical Team Leader, DMIP (*Meeting Chair*)

Sharon Thomas, Regulatory Project Manager, DMIP (*Meeting Recorder*)

**SPONSOR/APPLICANT:**

CBR International Corp. (Consultant for Piramal Imaging SA)

Jeanne M. Novak, PhD., CEO and Principal Consultant

Kevin Hennegan, MA, Senior Director of Clinical Affairs

**BACKGROUND:**

Piramal submitted an original NDA for florbetaben to FDA on December 21, 2012. Based on review of the original NDA, FDA issued an Information Request to Piramal on May 17, 2013. A Midcycle Communication Meeting took place on May 21 2013. On May 31, 2013, the Consultant contacted the Clinical Team Leader requesting clarification of action items post Midcycle Communication Meeting.

FDA called the sponsor and made the following points:

1. FDA referred Consultant to the discussions that took place at the Midcycle Communication Meeting and reminded Consultant of the FDA recommendation and sponsor's proposal, both expressed at the time, to submit materials presented by the sponsor at that meeting to the NDA (e.g. slides).
2. Submission of any additional supportive data or analyses is at discretion of the sponsor. In relation to clinical data, FDA has no additional information requests at this time. The clinical review of the NDA is ongoing.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no unresolved issues.

**ACTION ITEMS:**

None.

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

/s/  
-----

SHARON P THOMAS  
06/14/2013



NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

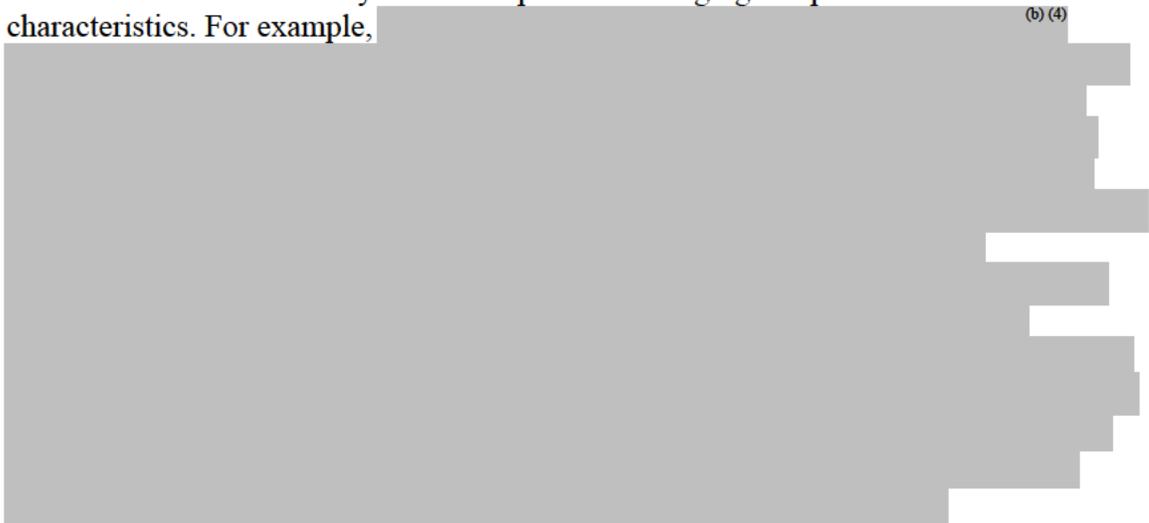
Dear Dr. Novak:

We make reference to your New Drug Application (NDA) for F-18 florbetaben. We have the following comments and information requests for the Post-Mid-cycle Communication Meeting:

1. We are concerned about the imaging performance characteristics (particularly specificity) of your product, as defined by comparison of imaging outcomes to a truth standard. Using the PET reading methodology proposed for future clinical practice, the five blinded readers, after being trained by the training DVD, achieved a specificity of 62.5 - 91.7%, with the lower bound of 95% confidence interval (CI) being as low as 43.1%. Four of the five blinded readers failed to reject the pre-specified null hypothesis on specificity (lower bound of 95% CI of specificity  $\leq 0.7$ ). In this regard, Study 16034 failed to achieve its objectives. The specificity decreased even further (both the point estimates and lower bound of 95% CI) when the 10 healthy volunteers were excluded. Even though the study won on the primary efficacy endpoint of inter-reader agreement, the five blinded readers appear to agree on the wrong thing with regard to specificity.
2. Since Study 16034 assesses how the product would perform in future clinical practice, this study bears greater clinical significance than Study 14595, which did not assess performance characteristics of the product using read methods simulating future clinical practice. For example, Study 14595 used a majority read of three independent readers in the primary efficacy analysis. However in clinical practice, most PET scans will be read by one reader, rather than the majority read of three readers. In addition, all subjects in Study 14595 had brain magnetic resonance imaging (MRI), and the blinded readers had the benefit of co-registered images of PET and MRI. There is little doubt that MRI offers superior image contrast between brain gray matter and white matter than PET (alone) imaging. Distinction between brain gray and white matter is a key requirement in Florbetaben PET image interpretation. However in current clinical practice, many centers in the U.S. may not have the capacity for PET-MRI imaging. Furthermore, blinded readers in Study 14595 had in-person training with additional feedback during the training. Therefore Study 14595 appears to show the product's bioactivity in localization of amyloid, based upon brain regional sensitivity and specificity calculations performed from non-clinically applicable imaging results. This bioactivity does not appear to have

translated into acceptable imaging test performance when images are interpreted using the clinically-applicable reader training method.

3. We understand that the proposed clinically-applicable PET reading methodology underwent multiple revisions during its development, and one of the early revisions appeared geared toward enhancing sensitivity, which apparently was achieved at the cost of specificity. We urge you to further refine the proposed PET reading methodology, including the training DVD, to enhance your product's imaging test specificity while retaining acceptable sensitivity. For example, perhaps a simpler binary reading methodology (somewhat similar to that used in Study 14595) has merit. Another suggestion would be to emphasize in the training DVD the importance of correctly interpreting PET images from patients without brain amyloid deposition (the training DVD does not appear to emphasize the importance of correctly interpreting amyloid-negative images). Perhaps other factors in the proposed clinically-applicable PET reading methodology could be refined to develop a robust reading methodology.
4. The product's proposed labeling (Sequence 9, April 15, 2013) appears to selectively cite clinical data that do not truly reflect the product's imaging test performance characteristics. For example,



At the upcoming meeting, we suggest you comment upon the imaging test performance deficiencies we cite above. In addition, we are requesting a formal response by May 30, 2013 to the following Chemistry comments and information requests:

5. Provide a table listing the doses of clinical trial product administered to patients for each generation of manufacturing process (1st, 2nd and 3rd) and formulation (development 1, 2 and 4). Include lot numbers, manufacture dates, synthesis module used, site, trial number and other pertinent information. Discuss the effect of manufacturing process changes on the product, including analytical methods, and the comparability to planned commercial product. Highlight clinical lots submitted in Module 3.2.P.5.4.02.
6. Provide additional information on the proposed commercial . We recommend that a Type V DMF be submitted by the  manufacturer. Refer to Guidance PET Drug Applications – Content and

Format for NDAs and ANDAs (August 2011) for the information to provide, which should include the following:

- Equipment description and principle of operation
  - Equipment specifications
  - Quality system information
  - Design Controls
  - Performance standards essential requirements
  - Design verification testing including programming logic / software testing
  - Safety margin testing
  - Equipment shelf-life
  - Risk assessment including Failure Mode, Effects and Criticality Analysis (FMECA)
  - Functional and electrical testing
  - Bench testing including extraneous environment testing.
  - Data for performance verification studies
  - Results of USP extractable study per chapter <381> and USP biological reactivity as per chapter <87> and chapter <88> on elastomeric components that come in contact with the drug
7. Similarly, provide a description of the [REDACTED] (b) (4) used to manufacture the lots of clinical product for which batch data were submitted. Discuss differences compared to the commercial [REDACTED] (b) (4) and their impact on product quality – including analytical methods.

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

/s/  
-----

RAFEL D RIEVES  
05/17/2013



NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act, for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq.

We are reviewing the Statistical section of your submission and have the following comments and information requests. At the present time, we are unable to verify the accuracy of the performance measures (sensitivity/specificity) that you cite in your proposed labeling. Our preliminary computations are raising questions about the sufficiency of your drug's efficacy data. We request a prompt written response to our requests in order to continue our evaluation of your NDA and to allow us to try to verify the accuracy of your proposed labeling claims (section 14 of labeling).

1. Please confirm that upid is usubjid (unique subject id).
2. For Study 14595, provide the detailed definitions for the SoTs (for primary and secondary analyses). Please confirm that "SoT" in the dataset effregv is used in the primary analyses.
  - SoT
  - SoT all: all amloid pathologies
  - SoT neur: neuritic plagues
  - SoT\_diff: diffuse plagues
  - SoT\_vasc: vascular amyloid
3. For Study 14595, provide xpt data, usubjid (upid), reader1 assessment, reader2 assessment, reader3 assessment, majority assessment, SoT, at subject level. Provide clear steps in word for generating the subject-level reads and SoT values by collapsing the regional results (and the sas codes for the steps).

4. For Study 14595, provide xpt data, usubjid(upid), reader1 assessment, reader 2 assessment, reader 3 assessment, majority read (based rules for future use); and SoT from on-site histopathology, at subject level.
5. For Study 16034, provide a xpt data including usubjid (upid), baseline clinical diagnosis, and SoT (either from autopsy, or assumed healthy subjects, or without SoT).

Please provide a response by e-mail to Ms. Sharon Thomas, Regulatory Project Manager at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, May 3, 2013 and follow-up with a formal amendment submission to the NDA.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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

/s/  
-----

RAFEL D RIEVES  
04/30/2013

---

**From:** Thomas, Sharon  
**Sent:** Wednesday, April 17, 2013 3:26 PM  
**To:** 'Kevin Hennegan'; 'Jeanne Novak'  
**Subject:** NDA 204677 – Florbetaben- Information Request- Clinical Pharmacology

NDA 204677

## **INFORMATION REQUEST**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act, for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq.

We have the following comments and requests for additional information:

1. Please provide comparative analyses of the sensitivity and specificity of SUVR relative to visual assessment using the full analysis data set for Study 16034 and histopathology as the Standard of Truth. We are interested in the relative performance at the level of individual reader as well as at the level of pooled read (3 of 5 readers). The analyses should include normal approximated confidence intervals.
2. Please repeat the above analyses excluding healthy volunteers from the data set.
3. Study 312161 appears to show that a 250 MBq dose yields adequate images. Is there justification for using 300 MBq rather than a dose of 250 MBq or lower?

Please provide a response by email to my attention: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov), by COB, Thursday, April 25, 2013 and follow-up with a formal amendment submission to the NDA.

If you have any questions, please don't hesitate to contact me.

*Sharon*

Sharon Thomas, RPM  
Division of Medical Imaging Products

Office of Drug Evaluation IV, CDER, FDA  
Phone: (301) 796-1994  
Fax: (301) 796-9849  
Email: [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov)

FDA does not ensure the security of email communications. For more information on establishing a Secure Electronic Mail link with CDER, contact [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov).

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

/s/  
-----

SHARON P THOMAS  
04/17/2013



NDA 204677

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Piramal Imaging SA  
c/o CBR International Corp  
2905 Wilderness Place,  
Suite 202  
Boulder, CO 80301

ATTENTION:           Jeanne M. Novak, Ph.D.  
                              Authorized Regulatory Representative and U.S. Agent

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated and received December 21, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Florbetaben 18F 300 MBq.

We also refer to your January 10, 2013, correspondence, received January 10, 2013, requesting review of your proposed proprietary name, Neuraceq. We have completed our review of the proposed proprietary name, Neuraceq, and have concluded that it is acceptable.

The proposed proprietary name, Neuraceq, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 10, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Sharon Thomas, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

/s/  
-----

CAROL A HOLQUIST  
04/10/2013

**From:** Nguyen, Thuy M  
**To:** ["Kevin Hennegan"](#)  
**Cc:** [Thomas, Sharon](#); ["Jeanne Novak"](#)  
**Subject:** Mr. Hennegan: NDA 204677 (Florbetaben): FDA Response - 04/03/13 re: Request for extension on submission of revised labeling  
**Date:** Wednesday, April 03, 2013 3:06:00 PM

---

Dear Mr. Hennegan,

Regarding NDA 204677 (Florbetaben), "extension request", the FDA looks forward to the revised labeling by April 15, 2013.

However, please response to the other items outlined in the Filing Letter by April 8, 2013.

Sincerely,  
Thuy M. Nguyen  
(covering for Ms. Sharon Thomas)  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
(301) 796-1427

---

**From:** Nguyen, Thuy M  
**Sent:** Wednesday, April 03, 2013 10:31 AM  
**To:** 'Kevin Hennegan'  
**Cc:** Thomas, Sharon; Jeanne Novak  
**Subject:** Mr. Hennegan: RE: NDA 20467 - Request for extension on submission of revised labeling

Dear Mr. Hennegan,

Thank you for the voice mail, 04/02 and email, 04/03.

Regarding [NDA 204677](#) (Florbetaben), "extension request", the Division's decision will be forwarded to you as soon as it becomes available.

Sincerely,  
Thuy M. Nguyen  
(covering for Ms. Sharon Thomas)  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
(301) 796-1427

---

**From:** Kevin Hennegan [mailto:khennegan@cbrintl.com]  
**Sent:** Wednesday, April 03, 2013 10:15 AM  
**To:** Nguyen, Thuy M  
**Cc:** Thomas, Sharon; Jeanne Novak  
**Subject:** NDA 20467 - Request for extension on submission of revised labeling

Dear Ms. Nguyen,

I am writing to follow up on the voice mail I left for you yesterday. Piramal Imaging has been

working on revisions to their proposed Prescribing Information according to the Agency's recommendations and comments included in the March 1, 2013 filing letter and earlier advice. We have received some additional internal feedback this week that we would like to incorporate before we supply our next draft to the Agency. May we request an extension of one additional week beyond the current due date (April 8) for our revised labeling and the accompanying justification document?

Thank you for your consideration. Please call me at [REDACTED] <sup>(b) (6)</sup> or Dr. Jeanne Novak at the CBR office, (720) 746-1190, if you would like to discuss this request.

Best regards,

Kevin

Kevin Hennegan, MA  
Senior Director of Clinical Affairs  
CBR International Corp. ®  
720-746-1190  
720-746-1192 (Fax)  
[www.cbrintl.com](http://www.cbrintl.com)

*This electronic transmission (including any and all attachments) is intended solely for the use of the individual or entity to whom it is addressed and may contain information that is privileged and/or confidential. If you are not the intended recipient of this electronic transmission, you are hereby notified that any disclosure, copying or distribution, or the taking of any action in reliance upon the contents of this electronic transmission, is strictly prohibited, and you are further requested to purge this electronic transmission and all copies thereof from your computer system.*

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

/s/  
-----

THUY M NGUYEN  
04/04/2013

From: Davis-Warren, Alberta E  
To: "[Kevin Hennegan](#)"  
Cc: [Thomas, Sharon](#); [Jeanne Novak](#); [Nguyen, Thuy M](#)  
Subject: RE: NDA 204677 - 120 day safety update inquiry  
Date: Wednesday, April 03, 2013 11:49:00 AM

---

Dear Kevin,

Please see the following comments regarding the 120 day safety report:

Please submit the 120 day report to the NDA by following the format outlined in the cited regulation and summarize all available safety information and if there are no additional safety data state so and explain. If there are no data to integrate you should state it in the submission, if there are new animal data state it in the submission etc. It could be a brief statement.

Please refer to 21CFR314.50(d)(5)(vi)(a) and 21CFR314.50(d)(5)(vi)(b) copied below for further information on the content and format of the report.

(vi) A summary and updates of safety information, as follows:

( a ) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

( b ) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)( a ) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports ( 1 ) 4 months after the initial submission; ( 2 ) in a resubmission following receipt of a complete response letter; and ( 3 ) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

Please contact me if you have any questions.

Thank you,  
Alberta  
Alberta E. Davis-Warren  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
301-796-3908 office  
301-796-9849 fax  
Alberta.Davis-Warren@fda.hhs.gov

*FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov).*

---

**From:** Kevin Hennegan [mailto:khennegan@cbrintl.com]  
**Sent:** Tuesday, April 02, 2013 3:04 PM  
**To:** Davis-Warren, Alberta E  
**Cc:** Thomas, Sharon; Jeanne Novak; Nguyen, Thuy M  
**Subject:** NDA 204677 -120 day safety update inquiry

Dear Alberta,

Thank you for speaking with Jeanne and I on Thursday. I hope you had a nice weekend. As discussed, we are evaluating the requirements/needs for Piramal Imaging to submit a 120 day safety update for their florbetaben NDA. To remind you of the current status of florbetaben clinical trials, the only study sponsored by Piramal that has been ongoing since the NDA was filed is the histopathology study (study 14595), and that trial is in the long-term follow up phase. Can you provide guidance as to whether a safety update should be submitted, and if so, what data and format should be included?

Thank you and best regards,

Kevin Hennegan, MA  
*Senior Director of Clinical Affairs*  
CBR International Corp. ®  
720-746-1190  
720-746-1192 (Fax)  
[www.cbrintl.com](http://www.cbrintl.com)

*This electronic transmission (including any and all attachments) is intended solely for the use of the individual or entity to whom it is addressed and may contain information that is privileged and/or confidential. If you are not the intended recipient of this electronic transmission, you are hereby notified that any disclosure, copying or distribution, or the taking of any action in reliance upon the contents of this electronic transmission, is strictly prohibited, and you are further requested to purge this electronic transmission and all copies thereof from your computer system.*

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

/s/  
-----

ALBERTA E DAVIS WARREN  
04/03/2013

From: Davis-Warren, Alberta E  
To: [Kevin Hennegan](#)  
Cc: [Jeanne Novak](#); [Thomas, Sharon](#)  
Subject: RE: Filing Letter- NDA 204677  
Date: Tuesday, March 26, 2013 5:39:00 PM

---

Dear Mr. Hennegan,

Below are FDA responses to your questions:

- Regarding Item 5 (Request for Table of Tables and Table of Figures in 311741 CSR), we propose to address the reviewer's request for a Table of Tables and Table of Figures by inserting these links as dedicated sections in the pdf bookmarks. We would prefer this approach to inserting pages into the body of the CSR, as it greatly reduces the labor required to recreate internal document hyperlinks. In addition, we believe that the bookmarks will actually be more useful to the reviewer, as the bookmark leaf can be continuously displayed while the reviewer is reading the text of the report. Is this approach acceptable?

**FDA response: Yes this is acceptable**

- Regarding Item 8 (Request for data regarding compound eluting at 17 min), we wanted to ensure that the reviewer is referring to the chromatograms in the clinical study report for study A42404 (starting on report page 223). The sponsor notes that the 17 min peak in the A42404 report was not described as florbetaben, so we wanted to verify we are discussing the same data before providing a response. Is the reviewer referring to the 17 min peak in the report for clinical study A42040?

**FDA response: We understand that the peak at 17 min is not the parent compound. We are interested in the identity and characterization of peak at 17 min in Study A42404 (starting on report page 223). We are also interested to know identity of the major peaks at 4.4 min and 4.8 minutes. The sponsor states that "The observation of two distinct peaks in preliminary plasma spiking experiments suggests that the polar metabolite is not 18F-PEGn3-OH."**

- Regarding Item 9 (Request for PK dataset), we wanted to ensure that the reviewer was aware that a PK dataset was provided in the original NDA in Module 5.3.5.3 (filename pkpd.xpt). Did the reviewer assess this file and still require additional information, or was this an issue of the reviewer not being able to find the dataset in the dossier?

**FDA response: Thank you for pointing out the PK data set. We appreciate it. Our request of March 1, 2013 was not for a PK/PD data set. We are seeking the entirety of results from each analytical run where patient samples were analyzed. That is, for each analytical run, we seek the results of the standard curve, QC samples, samples from patients, and blanks (if blanks were part of the run). The chronology of the run (i.e., when each type of sample was analyzed) is also requested.**

- Finally, regarding Item 10 (Request for *in vitro* amyloid binding data in human brain), we note that that a summary of amyloid binding data in human brain is provided in Module 2.4 – Non-Clinical Overview, section 2.1 (Primary Pharmacology). This data is presented in tabular format in Module 2.6.3, and full reports are provided in Module 4.2.1.1. Can you clarify what additional data the reviewer is looking for?

**FDA response: Thank you for identifying the location of the relevant data in the NDA. No additional data is requested.**

Please contact me if you have any questions.

Thank you

Alberta covering for Ms. Sharon Thomas

Alberta E. Davis-Warren

Regulatory Health Project Manager

Division of Medical Imaging Products

Office of Drug Evaluation IV

301-796-3908 office

301-796-9849 fax

Alberta.Davis-Warren@fda.hhs.gov

---

**From:** Kevin Hennegan [<mailto:khennegan@cbrintl.com>]

**Sent:** Thursday, March 21, 2013 3:04 PM

**To:** Thomas, Sharon

**Cc:** Jeanne Novak

**Subject:** RE: Filing Letter- NDA 204677

Dear Sharon,

Here are the additional questions/proposals:

- Regarding Item 5 (Request for Table of Tables and Table of Figures in 311741 CSR), we propose to address the reviewer's request for a Table of Tables and Table of Figures by inserting these links as dedicated sections in the pdf bookmarks. We would prefer this approach to inserting pages into the body of the CSR, as it greatly reduces the labor required to recreate internal document hyperlinks. In addition, we believe that the bookmarks will actually be more useful to the reviewer, as the bookmark leaf can be continuously displayed while the reviewer is reading the text of the report. Is this approach acceptable?
- Regarding Item 8 (Request for data regarding compound eluting at 17 min), we wanted to ensure that the reviewer is referring to the chromatograms in the clinical study report for study A42404 (starting on report page 223). The sponsor notes that the 17 min peak in the A42404 report was not described as florbetaben, so we wanted to verify we are discussing the same data before providing a response. Is the reviewer referring to the 17 min peak in the report for clinical study A42040?
- Regarding Item 9 (Request for PK dataset), we wanted to ensure that the reviewer was

aware that a PK dataset was provided in the original NDA in Module 5.3.5.3 (filename pkpd.xpt). Did the reviewer assess this file and still require additional information, or was this an issue of the reviewer not being able to find the dataset in the dossier?

- Finally, regarding Item 10 (Request for *in vitro* amyloid binding data in human brain), we note that that a summary of amyloid binding data in human brain is provided in Module 2.4 – Non-Clinical Overview, section 2.1 (Primary Pharmacology). This data is presented in tabular format in Module 2.6.3, and full reports are provided in Module 4.2.1.1. Can you clarify what additional data the reviewer is looking for?

Thank you for your assistance. I am available at any time today to discuss by phone if needed.

Best regards,

Kevin

Kevin Hennegan, MA  
Senior Director of Clinical Affairs  
CBR International Corp. ®  
720-746-1190  
720-746-1192 (Fax)  
[www.cbrintl.com](http://www.cbrintl.com)

*This electronic transmission (including any and all attachments) is intended solely for the use of the individual or entity to whom it is addressed and may contain information that is privileged and/or confidential. If you are not the intended recipient of this electronic transmission, you are hereby notified that any disclosure, copying or distribution, or the taking of any action in reliance upon the contents of this electronic transmission, is strictly prohibited, and you are further requested to purge this electronic transmission and all copies thereof from your computer system.*

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

/s/  
-----

ALBERTA E DAVIS WARREN  
03/26/2013

## TEAM MEETING MINUTES

March 5, 2013

NDA 204677

Neuraceq - Florbetaben F 18 Injection  
Sponsor - Piramal Imaging SA

---

**Submission Date:** December 21, 2012      **PDUFA Date:** December 21, 2013

**Proposed Indication:** 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.

**Meeting Purpose:** To discuss review discipline specific updates and to prepare for the upcoming mid-cycle meeting.

---

**Meeting attendees:** Rafel Rieves, Libero Marzella, Brenda Ye, Lan Huang, Jyoti Zalkikar, Gene Williams, Christy John, Erika Pfeiler, Sunny Awe, Sandra Rimmel, Cynthia LaCivita, Amarilys Vega, Eldon Leutzinger, Frank Lutterodt.

### 1. Review Discipline Updates

#### Clinical

- The review is ongoing.

#### Nonclinical

- No new updates, review is ongoing.

#### Statistics

- Sponsor submitted data sets that do not follow the data standard. Received help from OTS/office of computational science to solve the format error. Review is on-going.

#### Microbiology

- Under review, no updates. Response to the Information Request submitted on Feb 7<sup>th</sup> is under review.

#### Clinical Pharmacology

- Review is ongoing. May send an IR later during the week regarding correlation of SUVR vs visual read.

#### CMC

- Review is on-going No responses to comments submitted in the 74 day letter. The overall recommendation on the mfg facilities is pending.

However, three of the 6 facilities ( [REDACTED] (b) (4) ) are listed as acceptable. The other 3 sites [REDACTED] (b) (4) are still awaiting inspections.

OSE/Safety

- The Sponsor’s proprietary name, Neuraceq is currently under review. DMIP has no objections.

OSI

- [REDACTED] (b) (4) inspection will be completed by early May, still trying to schedule foreign inspections.

**2. Preparation for upcoming Mid-Cycle Meeting in May:**

Presentations (confirm who will/will not be presenting at the mid-cycle meeting)

- Clinical-- *Confirmed.*
- Statistical--*Confirmed.*
- Clinical Pharmacology-- *Will provide feedback by the end of the week.*
- Non-Clinical--*Confirmed.*
- CMC-- *Confirmed.*
- Micro- *Confirmed. Will present a few slides.*

**3. Milestones/Upcoming Meetings:**

| MILESTONES                        | MILESTONE DEADLINES | MEETINGS                                                |
|-----------------------------------|---------------------|---------------------------------------------------------|
| Receipt Date                      | Dec. 21, 2012       |                                                         |
| Day 45                            | Feb. 4, 2013        | <a href="#">Filing/Planning Meeting</a> Jan 29          |
| Day 60 (Filing Date)              | Feb. 19, 2013       |                                                         |
| Day 74 Letter Due                 | March 5, 2013       |                                                         |
| Spon Orientation Mtg              |                     | Feb. 4, 2013                                            |
| Team Meeting                      |                     | March 5, 2013 [Tues.]                                   |
| Team /Mid-Cycle Practice          |                     | April 11, 2013 [Tues.]                                  |
| Month 6- Mid-cycle Mtg.           | May 21, 2013        | <a href="#">Mid-cycle Meeting</a> May 15 [Wed]          |
| Mid-cycle –Communication Mtg.     | June 4, 2013        | <a href="#">Mid-cycle Comm Mtg</a> May 21 [Tues.]       |
| Team/Labeling Meetings            |                     | June 4, 2013 [Tues.]                                    |
|                                   |                     | June 11, 2013 [Tues.]                                   |
|                                   |                     | July 8, 2013 [Mon.]                                     |
|                                   |                     | July 16, 2013 [Tues.]                                   |
|                                   |                     | Aug 6, 2013 [Tues.]                                     |
| Send Labeling to Piramal          | By Aug, 21, 2013    |                                                         |
| Late Cycle Pre-Meeting            | Aug, 25, 2013       | <a href="#">Late Cycle PreMtg</a> Aug. 20, 2013 [Tues.] |
| Send Briefing Packages to Piramal | Sept. 4, 2013       | By Aug. 30, 2013 [Fri.]                                 |

|                                              |                         |                                          |
|----------------------------------------------|-------------------------|------------------------------------------|
| Issue DR Letters                             | Sept. 1, 2013<br>[Fri.] |                                          |
| Late Cycle Tcon with Piramal                 | Sept. 12, 2013          | LateCycle SponTcon Sept. 10, 2013[Tues.] |
| Wrap Up Meeting                              | Nov. 3, 2013            | Oct. 29, 2013 [Tues.]                    |
| OSI Clinical Inspection Summary Review       | Aug. 31, 2013           |                                          |
| Facility Inspections                         | Aug. 24, 2013           |                                          |
| OSE Review                                   | Aug. 23, 2013<br>[Fri.] |                                          |
| Primary Review due to TL                     | Aug. 23, 2013<br>[Fri.] |                                          |
| Secondary Review due to CDTL                 | Aug. 30, 2013<br>[Fri.] |                                          |
| DRISK Review/Memo                            | Sept. 3, 2013[Tue.]     |                                          |
| CDTL Review due to DD                        | Nov. 8, 2013<br>[Fri.]  |                                          |
| Division Director Review                     | Nov. 29, 2013<br>[Fri.] |                                          |
| Month 12 Goal Date Standard, Office Sign-off | Dec. 20, 2013<br>[Fri.] |                                          |

4. **Other items:** The application is scheduled for PeRC -Wed., July 10<sup>th</sup>.
- o RPM discussed upcoming milestones/meetings and confirmed PeRC meeting.

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

/s/  
-----

SHARON P THOMAS  
03/05/2013



NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq.

We are reviewing your NDA submission and have the following microbiology information requests/comments

1. Clarify whether drug product vials are intended for single or multiple patient use.
2. Your application states that you purchase the components of (b) (4). Provide a representative certificate of analysis from the manufacturer of these components indicating that they are provided (b) (4).
3. Your application does not describe sterilization methods for the drug product (b) (4). Describe sterilization methods for (b) (4). If the (b) (4) are provided sterile from the manufacturer, provide representative certificates of analysis from the (b) (4) manufacturers indicating that they are provided sterile.
4. State whether the drug product may be (b) (4) and under what conditions this (b) (4) may occur.
5. Your drug product specifications state that sterility testing is performed (b) (4). Sterility testing must be initiated within 30 hours of the completion of production (per 21 CFR 212.70(e)) unless a longer period of holding time has been validated. Update drug product specifications to reflect the time limit prior to testing, or provide validation data for a longer hold time.
6. Your application provides environmental monitoring (b) (4). Provide information for environmental monitoring that takes place during production, including sites monitored, methods of monitoring, monitoring schedule and alert/action levels.

Please provide a formal response by March 4, 2013. If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Danae Christodoulou, Ph.D.  
Acting Chief, Branch 7, Division 3  
Office of New Drug Quality Assessment  
CDER - FDA

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

/s/  
-----

DANAE D CHRISTODOULOU  
02/07/2013

**Filing/Planning Meeting  
January 29, 2013**

**NDA: 204677**

Product: Neuraceq (Florbetaben 18 Injection)  
Submission Date: December 21, 2012  
Received Date: December 21, 2012  
Sponsor: Piramal Imaging, SA (CBR International Corp./CRO)

**Proposed Indication:** 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.

1. Team Introductions

**Current Review Team for NDA 204677:**

Rafel Rieves, M.D., Director, DMIP  
Louis Marzella, M.D., Dep. Director, DMIP  
Sharon Thomas., Regulatory Health Project Manager, DMIP  
Brenda Ye, M.D., Medical Officer, DMIP  
Alex Gorovets, M.D., Ph.D. (TL and CDTL), DMIP  
Lan Huang, Ph.D., Statistics, DMIP  
Jyoti Zalkikar, Ph.D., Statistics (TL), DMIP  
Christy John, Ph.D., Clinical Pharmacology, DMIP  
Gene Williams, Ph.D, Clinical Pharmacology (TL), DMIP  
Sunny Awe, Ph.D., Non-Clinical, DMIP  
Adebayo Laniyonu, Ph.D., Non-Clinical (TL), DMIP  
Ann Marie Russell, Ph.D., Product, ONDQA  
Danae Christodoulou, Ph.D., Product (TL), ONDQA  
Erika Pfeiler, Ph.D. Microbiology Reviewer, OPS  
Bryan Riley, Ph.D. Microbiology (TL), OPS

2. Important dates

**Filing Date:** February 19, 2013

**Day 74 Letter:** March 5, 2013

**Mid-cycle:** May 15, 2013

**Primary Review due to TL:** August 23, 2013

**Secondary Review due to CDTL:** August 30, 2013

**CDTL Review due to DD:** Nov. 8, 2013

**Division Director Review:** Nov. 30, 2013

**Month 12 Goal Date Standard, Office Sign-off:** December 21, 2013

**Review Status:**

- Standard Review - confirmed- (12 month clock) PDUFA V

Review Program

- Categorical Exclusion requested
- Sponsor requested full waiver of pediatric studies – triggers PREA
- Sponsor requested waiver for carcinogenicity studies

**DISCUSSION:** RPM discussed the review status and important dates indicated above.

3. Overview of Application by Discipline: Studies/info submitted; identification of Info Requests; Day 74 letter items or RTF issues

- a. Clinical: Fileable- Yes-** No filing issues identified. The following clinical comments were conveyed in an Advice/Information Request (IR) letter dated 1/18/13.
1. The Pivotal Phase 3 study 14595 appears to only have an interim clinical study report and an addendum of additional safety analysis only. Please provide the final clinical study report of the study and submit to the NDA as one complete report.
  2. More than half of subjects included in the pivotal ‘pooled read’ study came from study 311741, yet the clinical study report of #311741 (A45264) lacks “Table of Tables” and “Table of Figures”. This significantly hinders our review process. Please revise the clinical study report A45264 to include “Table of Tables” and “Table of Figures” with electronic links to individual tables and figures and resubmit to the NDA.
  3. Since more than half of subjects included in the pivotal ‘pooled read’ study came from study 311741, please submit clinical site information for study #311741 as you did for study 14595. Include pertinent information such as the number of subjects enrolled, completed, analyzed, and discontinued at each clinical site and the number of protocol violations at each clinical site.

**DISCUSSION:** The sponsor will address the clinical comments/‘pooled read’ study in the upcoming Applicant Orientation Meeting.

**b. Stats: Fileable- Yes-** Comments to be submitted in the January 29<sup>th</sup> Information Request:

1. When we load your xpt files into sas, many variables do not have the right format. The error message is “Format was not found or could not be loaded”. Please provide the format for all the data submitted.
2. Provide the names of the data sets and the related sas programs used to generate the tables in the submission, especially the tables for the efficacy evaluation in studies 14595 and 16034.

3. According to the sponsor, the images to be assessed during this pooled read study (Study 16034) were chosen from various Phase 1 studies, the Phase 2 study (Part B) and Phase 3 study. Provide clear picture of the subjects from all the earlier studies and the rationale to include them in the pooled read study.

*(For interim analysis:*

*The initial period of the study pivotal for first submission to the regulatory agencies, was to end after at least 30 histological specimens were available.*

*Need to ask for clarification (type I error control and DSMB minutes).*

**DISCUSSION:** The sponsor agreed to address the statistical IR during the Applicant Orientation Meeting and follow-up with a formal response to the NDA.

- c. P/T: Fileable –Yes-**the NDA is fileable from nonclinical perspective.

**DISCUSSION:** P/T reviewer noted that the sponsor’s waiver request from carcinogenicity studies was granted in Oct., 2012.

- d. CMC – Fileable Yes-** the NDA is fileable.

**DISCUSSION:** CMC/Eldon Leutzinger will assist with the following items:

- Establishment (EES)/Coordinate Inspections
- Environmental Analysis: Request for Categorical Exclusion
- Labeling

- e. Micro – Fileable – Yes.**

**DISCUSSION:** Micro reviewer will forward RPM comments to include in the Day 74 letter.

4. Potential Consults/Collaborative Reviewers Needed:

|                 |                                                                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| OPDP            | Jim Dvorsky                                                                                                                                                                                     |
| OSE             | Sandra Rimmel-OSE RPM<br>Kevin Wright -OSE Reviewer<br>Yelena Maslov-OSE TL<br><br>DMEPA/CMC/DDMAC to review PI and carton/container labeling.<br><br>Proprietary Name Review - <i>Neuraceq</i> |
| Maternal Health | Not Needed                                                                                                                                                                                      |
| Peds            | Not Needed                                                                                                                                                                                      |
| Facility/OMPQ   |                                                                                                                                                                                                 |
| OSI             | Due February 4 <sup>th</sup>                                                                                                                                                                    |
| PeRC            | <b><i>The application scheduled for PeRC on July 10th</i></b>                                                                                                                                   |
| Neurology       | Not Needed                                                                                                                                                                                      |
| AC              | No AC Meeting                                                                                                                                                                                   |

**DISCUSSION:** Standard review confirmed. RPM noted that the sponsor’s proposed proprietary name “Neuraceq” is under review with DMEPA. PeRC scheduled July 10th, 2013. No need for Maternal Health, Peds labeling consults. No neurology consult needed. No AC meeting.

5. Applicant Orientation Presentation:

**DISCUSSION:** RPM reminded team of upcoming NDA Orientation Meeting, Monday, February 4, 2013. During this meeting, the sponsor will focus on the reader training methodology, labeling and statistical items.

6. Miscellaneous Items or Issues:

**DISCUSSION** – Clinical TL noted that the OSI, site selection and scheduling is in progress. RPM noted that the consult is due on February 4, 2013.

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

/s/  
-----

SHARON P THOMAS  
02/01/2013



NDA 204677

## INFORMATION REQUEST

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq.

We are reviewing your NDA submission and have the following information requests/comments:

1. When we load your xpt files into sas, many variables do not have the right format. The error message is "Format was not found or could not be loaded". Please provide the format for all the variables in all the data submitted. You may need to resubmit all the xpt files to correct this problem. Failure to promptly resolve this problem may preclude our ability to review your application in a timely manner.
2. Provide the names of the data sets and the related sas programs used to generate the tables in the submission, especially the tables for the efficacy evaluation in studies 14595 and 16034.
3. The images to be assessed during the "pooled read" study (Study 16034) were chosen from various Phase 1 studies, the Phase 2 study (Part B) and the Phase 3 study. Provide a description of the criteria you used to select images/subjects for inclusion in the pooled read study. Were these criteria pre-specified in a manner that clearly identified which images/subjects would be included/excluded from the pooled read? If so, provide the documentation that verifies these details of the image/subject selection process. Also provide a table (or figure) that describes the Study 16034 subject distribution (by the study that originally enrolled the subject).
4. Regarding Study 14595, we have been unable to locate the pre-specified statistical analytical plan (SAP). Please identify the location of the SAP and/or submit this plan. We are particularly interested in the details of the interim analysis.

Please address the above items at the Applicant Orientation Meeting on February 4, 2013 and follow-up with a formal response as a submission to your NDA within seven days following receipt of this letter.

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

/s/  
-----

RAFEL D RIEVES  
01/29/2013



NDA 204677

**GENERAL ADVICE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Florbetaben (BAY 94-9172) Solution for Injection 300 MBq.

We are reviewing your NDA submission and have the following requests/recommendations for the Applicant Orientation Meeting on February 4, 2013:

1. It appears from the NDA submission that the Florbetaben PET reading methodology continually evolved through Phase 1, Phase 2, and Phase 3 studies. It helps the FDA review team if you present the evolution of the reading methodology used in each of the stages, and explain the rationale of changes at each step. In particular:
  - Present the evolution of the Regional Cortical Tracer Binding (RCTB)/Regional Cortical Tracer Uptake (RCTU) algorithms and the brain  $\beta$ -amyloid plaque load (BAPL) scoring system through various studies, including between Part A and Part B of the Phase 2 Study #311741
  - Demonstrate the reasons for the inclusion of 4 cortical regions and the exclusion of other brain regions that originally explored in previous studies
2. Step-by-step demonstrate the proposed Florbetaben PET reading methodology, including assigning regional scores (RCTB/RCTU) through the final composite score (subject level BAPL). Demonstrate the reading methodology step-by-step with at least one case from each of the following categories:
  - Easy normal
  - Easy abnormal
  - Difficult normal (or demonstrate ranges of normal)
  - Difficult abnormal (or demonstrate ranges of abnormal)
3. Rainbow color display was used in Phase 1 and Phase 2 studies, while gray scale display was used in Phase 3 studies and appears to be proposed for future clinical use as well. Please discuss the rationale of your transition from rainbow color display to gray scale display. If helpful, you may use case presentations to illustrate your points.
4. Explain why only transverse (trans-axial) images were used throughout the evolution of the Florbetaben PET reading methodology, leaving out coronal and sagittal images. It is

conceivable that some imaging centers may have PET images displayed in 3 planes. Please justify training readers to read only the transverse (trans-axial) images.

5. The primary efficacy analysis of the ‘Histopathology’ study (#14595) was based on regional analysis of 6 brain regions. The proposed Florbetaben PET reading methodology assesses 4 brain regions, most of which appear different from the 6 brain regions used for the primary efficacy analysis of the ‘Histopathology’ study. Please explain the difference in the selection of brain regions for these two studies, and present justifications for the 4 brain regions chosen for the PET reading methodology.
6. The proposed Florbetaben PET reading methodology designates two levels of positive read – moderate amyloid deposition and pronounced amyloid deposition. Please discuss clinical implications/distinctions, if any, between the two positive levels.
7. We are very concerned about your proposed labeling and suggest you promptly revisit this proposal and submit revised labeling, if necessary. We also suggest you address these matters at the upcoming meeting. We suggest you examine the labeling we required for the currently approved amyloid-imaging agent and consider revision of your proposed labeling to build upon this precedent. Multiple aspects of your current labeling proposal represent problems that must be resolved. Below we list the items that initially signaled concerns. We have not performed a thorough review of your labeling but based upon these obvious problems, we are very concerned that your labeling proposal needs extensive revision.

- a.
- b.
- c.
- d.
- e.
- f.
- g.

(b) (4)

h.

(b) (4)

If you have any questions, call Ms. Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Rafel Dwaine Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

/s/  
-----

SHARON P THOMAS  
01/18/2013

RAFEL D RIEVES  
01/18/2013



NDA 204677

**NDA ACKNOWLEDGMENT**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Florbetaben (BAY 94-9172) Solution for Injection 300 MBq

Date of Application: December 21, 2012

Date of Receipt: December 21, 2012

Our Reference Number: NDA 204677

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Medical Imaging Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, BSc, RHIT, CCRP  
Project Management Staff  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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

/s/  
-----

SHARON P THOMAS  
12/31/2012



IND 78868

**MEETING MINUTES**

Bayer HealthCare Pharmaceuticals, Inc.

Attn: [REDACTED] (b) (4)

Dear Ms. [REDACTED] (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAY 94-9172 (AVI-ZK) (Florbetaben).

We also refer to the telecon between representatives of your firm and the FDA on August 24, 2012. The purpose of the pre-NDA meeting was to discuss the content and format of the NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Sharon Thomas, B.Sc., CCRP  
Regulatory Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

**Enclosure:  
Meeting Minutes**

## TELECONFERENCE MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** August 24, 2012, 1:00 PM  
**Meeting Location:** WO Building 22, Room 2201

**Application Number:** IND 78,868  
**Product Name:** Florbetaben (BAY 94-91721 AV1-ZK)

**Sponsor/Applicant Name:** Bayer HealthCare Pharmaceuticals

### FDA ATTENDEES:

#### Division of Medical Imaging Products (DMIP)

Charles Ganley, M.D., Director, ODE IV  
Rafel D. Rieves, M.D., Division Director, DMIP  
Liberio Marzella, M.D., Ph.D., Deputy Division Director, DMIP  
Lucie Yang, M.D., Ph.D., Clinical Team Leader, DMIP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIP  
Brenda Ye, M.D., Medical Officer, DMIP  
Anthony Mucci, Ph.D., Acting Team Leader Statistics, OB/DBV  
Lan Huang, Ph.D., Statistical Reviewer, OB/DBV  
Jyoti Zalkikar, Ph.D., Statistical Supervisor, OB/DBV  
Eldon Leutzinger, Ph.D., Pre-Marketing Branch Chief, ONDQA  
Ali Al Hakim, Ph.D., Pre-Marketing Branch Chief, ONDQA  
Sunny Awe, Ph.D., Pharmacology/Toxicology Reviewer, DMIP  
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPV  
Robert Mello, Ph.D., Microbiology Reviewer, OPS/NDMS  
Sunny Awe, Ph.D., Pharmacology/Toxicology Reviewer, DMIP  
Sharon Thomas, Sr. Regulatory Health Project Manager, DMIP

### SPONSOR ATTENDEES:

Bayer HealthCare Pharmaceuticals

(b) (4)

Ulrike Bodesheim, PhD, MDRA, Lead Global Regulatory Strategist  
Christine Becker, MS., Head Global Regulatory Affairs, Diagnostic Imaging  
Cornelia Reininger, M.D., Ph.D., Global Clinical Development  
Barbara Putz, M.D., Ph.D., Global Clinical Development  
Jens Leopold, Ph.D., Group Head Regulatory Affairs CMC  
Torsten Zimmerman, Ph.D., Lead Clinical Pharmacologist  
Cordula Hopmann, Ph.D., Global Project Management  
Michael Kunz, PhD, Global Clinical Development/Global Clinical Statistics  
Tatyana Kovtun, Global Clinical Development/Clinical Data Center

Patty Hegarty, Global Clinical Development/Global Clinical Statistics  
Andrew W. Stephens, M.D., Ph.D., Head Clinical Research and Development

(b) (4)  
Jeanne M. Novak, Ph.D., CEO, CBR International Corp, Future US Agent and Regulatory

Representative for Piramal

Dana Weinberger, Ph.D., CBR International Corp., Regulatory Affairs

**1.0 OBJECTIVE:**

To discuss the NDA format and content.

**2.0 BACKGROUND:**

The purpose of the meeting between FDA and Bayer was to discuss florbetaben, now at the pre-NDA stage of development. The proposed indication is the “(b) (4)” Bayer has entered into an agreement to sell Florbetaben to Piramal Imaging SA in December 2012. Piramal plans to submit the NDA by the end of 2012.

**3.0 DISCUSSION**

DMIP provided preliminary comments to Bayer on August 23, 2012 in response to Bayer’s questions in their meeting briefing package dated July 7, 2012. Bayer responded via email on August 24, 2012, indicating the questions/responses requiring further discussion at the meeting (Attachment 1) and providing additional comments and revised proposals as the basis for further discussion. The original questions provided by the sponsor are presented in italics, followed by FDA’s preliminary responses in bold text. The MEETING DISCUSSION points are shown in ***bold italics*** below

**MEETING QUESTIONS**

**CLINICAL**

**Sponsor’s Question 1:**

*Does FDA agree with the placement of these pivotal studies in the eCTD structure of Module 5 in section 5.3.5.1?*

**FDA Response:**

**We agree.**

**MEETING DISCUSSION: *This question was not discussed.***

**Sponsor’s Question 2:**

*Does the FDA concur with Bayer’s justification for pooling the safety data in the described approach?*

**FDA Response:**

**We concur.**

**MEETING DISCUSSION:** *This question was not discussed.*

**Sponsor's Question 3:**

*Does the FDA concur with Bayer's approach to the extent and placement of the ISE within the NDA submission?*

**FDA Response:**

**We concur with Bayer's approach to the extent and placement of the ISE within the NDA submission and recommend providing a statement in the Module 5 indicating the location of the narrative portion of the ISE.**

**MEETING DISCUSSION:** *This question was not discussed.*

**Sponsor's Question 4:**

*Does the FDA concur with Bayer's approach to the extent and placement of the ISS within the NDA submission?*

**FDA Response:**

**We concur with Bayer's approach to the extent and placement of the ISS within the NDA submission and recommend providing a statement in the Module 5 indicating the location of the narrative portion of the ISS.**

**MEETING DISCUSSION:** *This question was not discussed.*

**STATS**

**Sponsor's Question 5:**

*Does the FDA agree with the proposal outlined above regarding the scope, format, and documentation of the electronic datasets to be submitted?*

**FDA Response:**

**We agree. Given the pending transition of the product to Piramal, we would like to emphasize and request that each summary table in the clinical study reports (phase 1, phase 2, phase 3, ISS, ISE) contains an electronic link to the underlying SAS datasets.**

**MEETING DISCUSSION:**

*Bayer explained that the study reports were complete and they would submit the data for verification with the NDA. Bayer confirmed that the tables would include an identifier in the footnote. Bayer agreed to submit SAS datasets for phases 2 and 3 studies, as well as the datasets necessary to verify analyses described within the ISS/ISE. FDA requested submission of datasets also for phase 1 studies and Bayer agreed to follow-up with the CRO to obtain the phase 1 data sets. FDA expressed the importance of the SAS datasets to verify the results.*

***FDA noted that CDER's preferred method of submission is via the Electronic Submissions Gateway (ESG). Bayer noted that Piramal would submit the NDA [REDACTED] (b) (4) [REDACTED]. Bayer/Pramal confirmed that the NDA would be a full electronic submission.***

**See ADDITIONAL FDA COMMENTS – CLINICAL PHARMACOLOGY**

**CMC**

**Sponsor's Question 6:**

***Does the FDA agree with the proposed two sections 3.2.S, one for the [REDACTED] (b) (4) [REDACTED] and a second one for the active ingredient florbetaben in Module 3?***

**FDA Response:**

**We agree.**

**MEETING DISCUSSION: *This question was not discussed.***

**REGULATORY**

**Sponsor's Question 7:**

***Does the Agency anticipate requesting an Applicant Orientation Meeting for the Florbetaben NDA?***

**FDA Response:**

**Yes, we anticipate requesting an Applicant Orientation Meeting for the Florbetaben NDA. A portion of the meeting will be devoted to the MEETING DISCUSSION of the reader training program. We have reviewed the reader training program installed on a laptop, and we will send you our comments on the training program under a separate cover.**

**MEETING DISCUSSION: *This question was not discussed.***

**Sponsor's Question 8:**

***After review of the Information Package, has the Agency identified any issues that may affect the filing or review of the NDA?***

**FDA Response:**

**It is premature to comment at this time.**

**MEETING DISCUSSION: *This question was not discussed.***

**ADDITIONAL FDA COMMENTS:**

**CMC:**

**At the time of submission of the NDA:**

1. **There must be a statement that all sites involved in the manufacture and testing of the finished drug product are ready for CGMP inspection, per 21 CFR 212.**

**MEETING DISCUSSION:**

*Bayer agreed to provide a “ready for CGMP inspection” statement in Module 1.*

*FDA requested a complete list of contact information for all manufacturing sites listed within the NDA, including the name of the company, street address, city, postal/zip code, and contact person for the facility inspections with name, email, and telephone number. Bayer agreed.*

2. **The NDA must contain stability data for 3 batches, representative of production batches, at the highest radioactivity concentration proposed. These batch data should be for batches packaged in the proposed container-closure system and at the proposed storage conditions.**

**MEETING DISCUSSION:**

*Bayer agreed to submit the stability data in Module 3.2.P.*

**MICROBIOLOGY:**

**Microbiological product quality information, specific for each site, should be submitted in the NDA including, but not necessarily limited to, the following:**

3. **Facility description information (floor plans and/or a narrative describing the general layout as well as the location of critical equipment).**
4. **Information on viable environmental monitoring (air, surface, personnel) procedures (and frequencies) supporting the (b) (4) drug manufacturing processes.**
5. **Media fill procedures and summary data supporting the (b) (4) drug manufacturing processes such as the preparation of (b) (4)**

**For guidance on this topic, we refer you the Agency's 2012 guidance on this topic which may be obtained online at (b) (4)**

**MEETING DISCUSSION:**

*Bayer agreed to submit the above information in NDA Module 3.2.A.*

**NONCLINICAL:**

6. We noted that you have not submitted reproductive and developmental toxicity data on Florbetaben. Please provide the data or request for a waiver from conducting the studies with adequate justifications.

**MEETING DISCUSSION:**

*Bayer agreed to submit a waiver request to the IND from conducting developmental toxicology studies with appropriate justification.*

7. Your request for a waiver from conducting carcinogenicity studies on Florbetaben has been granted.

**MEETING DISCUSSION:** *This question was not discussed.*

**CLINICAL PHARMACOLOGY:**

8. Please include the following three electronic datasets and “Highlights of Clinical Pharmacology” table in the NDA

A. A single dataset containing all of the raw QT data contributing to the NDA. The file should include (each item is a column):

- 1) Clinical study number
- 2) Subject ID
- 3) Dose (nominal, units of mass/kg bw)
- 4) Dose (actual -- units of mass)
- 5) Time (nominal time pre- or post-dose)
- 6) Time (actual time pre- or post-dose)
- 7) Actual QT (units of ms)
- 8) QTc (units of ms)
- 9) Categorical variable stating correction method (e.g., Fredricia's)
- 10) Whether subject was sampled for PK
- 11) Separate columns for each subject's demographic data (sex, weight, age) and other variables potentially influencing QT (as available -- cardiac risk factors, concomitant medications, other factors identified by Bayer) should be included and be repeated for each row of the dataset
- 12 (and subsequent) Other information as Bayer desires to include

B. A single dataset containing all of the raw concentration data contributing to the PK analyses, and PD data, in the submission. The file should include (each item is a column):

- 1) Clinical study number
- 2) Subject ID
- 3) Dose (nominal, units of mass/kg bw)
- 4) Dose (actual -- units of mass)

- 5) Time (nominal time pre- or post-dose)
  - 6) Time (actual time pre- or post-dose)
  - 7) Conc (units of mass/volume)
  - 8) Separate columns for each subject's demographic data (sex, weight, age) and other variables potentially influencing PK (as available -- creatinine clearance, liver chemistries, disease states, other factors identified by Bayer) should be included and be repeated for each row of the dataset
  - 9) Separate columns for each subject's PD data (SUV, imaging outcome, other information as Bayer desires to include)
  - 10 (and subsequent) Other information as Bayer desires to include
- C. A single dataset containing all of the raw data from the analytical runs for all samples contributing to PK analysis. The file should include (each item is a column):
- 1) Clinical study number
  - 2) Calendar date of analysis of the sample ("sample" includes blanks, standards, QCs -- all determinations included in the analytical run)
  - 3) Clock time of analysis of the sample
  - 4) Categorical variable describing sample type -- blank, standard, QC, subject data, re-analysis, dilution
  - 5) For subject data only (column is empty for non-subject samples) -- subject ID, nominal post-dose sample time, actual post-dose sample time (these could be split into separate columns if desired)
  - 6) For subject data only (column is empty for non-subject samples and for samples that are not dilutions) -- the degree (x-fold) of dilution
  - 7 (and subsequent) Other information as Bayer desires to include
9. "Highlights of Clinical Pharmacology" table. This format is a boilerplate used by the Interdisciplinary Review Team for QT (the IRT). Selected items may be inapplicable to your intravenously administered drug product.

| Highlights of Clinical Pharmacology       |                                                                  |                                      |
|-------------------------------------------|------------------------------------------------------------------|--------------------------------------|
| Therapeutic dose                          | Include maximum proposed clinical dosing regimen                 |                                      |
| Maximum tolerated dose                    | Include if studied or NOAEL dose                                 |                                      |
| Principal adverse events                  | Include most common adverse events; dose limiting adverse events |                                      |
| Maximum dose tested                       | Single Dose                                                      | Specify dose                         |
|                                           | Multiple Dose                                                    | Specify dosing interval and duration |
| Exposures Achieved at Maximum Tested Dose | Single Dose                                                      | Mean (%CV) Cmax and AUC              |
|                                           | Multiple Dose                                                    | Mean (%CV) Cmax and AUC              |
| Range of linear PK                        | Specify dosing regimen                                           |                                      |
| Accumulation at steady state              | Mean (%CV); specify dosing regimen                               |                                      |
| Metabolites                               | Include listing of all metabolites and activity                  |                                      |
| Absorption                                | Absolute/Relative                                                | Mean (%CV)                           |

|                                                 |                                                                                                                                                  |                                                                                                                         |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
|                                                 | <b>Bioavailability</b>                                                                                                                           |                                                                                                                         |
|                                                 | <b>Tmax</b>                                                                                                                                      | <ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul> |
| <b>Distribution</b>                             | <b>Vd/F or Vd</b>                                                                                                                                | Mean (%CV)                                                                                                              |
|                                                 | <b>% bound</b>                                                                                                                                   | Mean (%CV)                                                                                                              |
| <b>Elimination</b>                              | <b>Route</b>                                                                                                                                     | <ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>      |
|                                                 | <b>Terminal t<sub>1/2</sub></b>                                                                                                                  | <ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>         |
|                                                 | <b>CL/F or CL</b>                                                                                                                                | Mean (%CV)                                                                                                              |
| <b>Intrinsic Factors</b>                        | <b>Age</b>                                                                                                                                       | Specify mean changes in Cmax and AUC                                                                                    |
|                                                 | <b>Sex</b>                                                                                                                                       | Specify mean changes in Cmax and AUC                                                                                    |
|                                                 | <b>Race</b>                                                                                                                                      | Specify mean changes in Cmax and AUC                                                                                    |
|                                                 | <b>Hepatic &amp; Renal Impairment</b>                                                                                                            | Specify mean changes in Cmax and AUC                                                                                    |
| <b>Extrinsic Factors</b>                        | <b>Drug interactions</b>                                                                                                                         | Include listing of studied DDI studies with mean changes in Cmax and AUC                                                |
|                                                 | <b>Food Effects</b>                                                                                                                              | Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)                                  |
| <b>Expected High Clinical Exposure Scenario</b> | Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. |                                                                                                                         |

**MEETING DISCUSSION:**

*Bayer agreed to provide the single dataset containing QT data and PK analyses. FDA requested Bayer to submit pharmacodynamic data including SUV, SUVR calculations in HV, MCI, AD and visual assessment generated as part of phase 1, phase 2, and phase 3 studies.*

**4.0 ISSUES REQUIRING FURTHER DISCUSSION:**

**FDA’s Advice/Information Request Letter dated August 16, 2012 (response to Bayer’s July 23, 2012 submission containing the “Pooled Read Study,” Statistical Analysis Plan and Imaging Charter).**

**Comment #1**

**You are proposing an imputation method for “not assessable” images in the primary and secondary analyses. We recommend using a “forced decision” rule and record the reader’s confidence in the decision.**

**MEETING DISCUSSION:**

*Bayer noted that in the phase 2 and histopathology studies, the “not assessable” images were less than one percent. FDA stated that the imputation schemes were unclear. FDA emphasized the importance of a forced decision in all cases. Bayer stated that all the images have been interpreted by the readers. The readers can not read the images again with the force-decision rule. FDA asked for clarification of the primary endpoint kappa—specifically the subject population. Bayer stated that the kappa coefficient for the primary analysis was based on all images. FDA asked whether datasets will allow an assessment of how often imputation was necessary. Bayer responded affirmatively. Bayer agreed to submit this information in the NDA.*

**Comment #2**

**We do not fully understand how you have arrived at the proposed sample size and, at the same time, how well you have provided for your study to include a full clinical variety of patients who would be undergoing imaging with the use of your drug in clinical practice. In particular, we strongly recommend including an adequate number of patients with MCI to properly evaluate reader agreement in this clinically important subgroup (by kappa statistic and percent agreement).**

**MEETING DISCUSSION:**

*Bayer referred to a previous clinical study that contained a broad range of subjects including subjects with probable/possible AD, MCI, dementia sub-types other than AD, HV (> 55 and < 40 years). Bayer noted that the older healthy controls included subjects 80 years of age or older.*

*Bayer explained that there was a re-read of certain Phase 2b study images and these details will be described in the NDA. Bayer briefly discussed some of the phase 3 study subset analyses, including the MCI subset.*

*FDA inquired about the definition of non-demented volunteers and how they differed from healthy volunteers. Bayer agreed to provide definitions for these subject descriptors.*

**Comment #3**

**You propose including ten healthy younger volunteers in analyses of sensitivity and specificity. We recommend not including these patients.**

**MEETING DISCUSSION:**

*Bayer confirmed that they would include the HV PET scans in the phase 3 pivotal study (#14595) and also would include the HV PET scans in the Pooled Read study. Bayer noted that the power calculation for Study 14595 specificity was calculated including the 10 HV PET scans.*

*For the phase 3 studies, FDA requested exploratory performance characteristics (sensitivity/specificity) and reproducibility analyses of a sub-group that excludes HVs. Bayer concurred.*

**Comment #4**

**You propose obtaining normal approximated 95% confidence intervals for analyses of sensitivity and specificity. We recommend using exact confidence intervals.**

**MEETING DISCUSSION:**

*Bayer agreed with the FDA's recommendation to implement exact confidence intervals.*

**Comment #5**

**In the submitted Imaging Charter, we find no provisions for a possible replacement of a reader. You may wish to pre-specify the circumstances that might lead to reader replacement and propose that a new reader would read the entire set.**

**MEETING DISCUSSION**

*Bayer stated that the blinded read of the Pooled Image Read Study had been completed. No reader replacement was necessary during the course of the study.*

**5.0 ACTION ITEMS:**

- Bayer to submit a document that defines the subject descriptor terms, “non-demented” and “healthy volunteer,” including any difference in these descriptors.

**6.0 ATTACHMENTS AND HANDOUTS:**

- Bayer's slides (August 24, 2012) to FDA's responses and comments.

18 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/  
-----

SHARON P THOMAS  
09/20/2012

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



**NDA 204677**

**LATE-CYCLE MEETING MINUTES**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Neuraceq (Florbetaben F 18) Injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 10, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please feel free to contact Ms. Sharon Thomas, Regulatory Project Manager at (301) 796-1994 or via email at [sharon.thomas@fda.hhs.gov](mailto:sharon.thomas@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** September 10, 2013  
**Meeting Location:** White Oak, Bldg. 22, Conf. Room 1421

**Application Number:** NDA 204677  
**Product Name:** Neuraceq (Florbetaben F 18 Injection)  
**Applicant Name:** Piramal Imaging, SA

**Meeting Chair:** Alex Gorovets, M.D.  
**Meeting Recorder:** Sharon Thomas, RPM

**FDA ATTENDEES**

Shaw Chen, MD, PhD, Deputy Director, ODE IV  
Libero Marzella, MD, PhD, Director (acting), Division of Medical Imaging Products (DMIP)  
Alex Gorovets, MD, Clinical Team Leader, DMIP  
Jagjit Grewal, Acting ADRA, ODE IV  
Brenda Ye, MD, Primary Reviewer, DMIP  
Eldon Leutzinger, PhD, CMC Lead, ONDQA  
Anne Marie Russell, PhD, CMC Reviewer, ONDQA  
Danae Christodoulou, PhD, Branch Chief Acting, ONDQA  
Eric Duffy, PhD, Division Director, ONDQA  
Jyoti Zalkikar, PhD, Statistical Team Leader, OB/DBV  
Lan Huang, PhD, Statistical Reviewer, OB/DBV  
Sunny Awe, PhD, Pharm/Tox Reviewer, DMIP  
Gene Williams, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCP5  
Christy John, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP5  
CDR Sandra Rimmel, OSE Regulatory Project Manager  
Kevin Wright, Pharm D, DMEPA reviewer  
Michael Kieffer, Reviewer, OSE – Pharmacovigilance  
Peter Diak, Team Leader, OSE – Pharmacovigilance  
Adora Ndu, PhD, Reviewer- OPDP  
Amarilys Vega, MD, MPH, DRISK reviewer  
Sharon Thomas, BSc, Sr., Regulatory Project Manager, DMIP

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (6), Independent Assessor

**APPLICANT ATTENDEES**

Kelly Bechter, Regulatory Associate. CBR International  
Ana Catafau, MD, PhD, VP Clinical Research and Dev Neurosciences, Piramal Imaging  
Ludger Dinkelborg, CEO, Piramal Imaging

Kevin Hennegan, MA, Senior Director of Clinical Affairs, CBR International  
Jürgen Hirschfeld, PhD, Senior Director Regulatory Affairs, Piramal Imaging  
Norman Koglin, PhD, Director Portfolio Management, Piramal Imaging  
Andre Mueller, PhD, Director Radiopharmacology, Piramal Imaging  
Andrew Stephens, MD, PhD, VP Clinical Research and Development, Piramal Imaging

(b) (4)  
Christian Schmidt, PhD, Head CMC Operations, Piramal Imaging

(b) (4) Consultant, CMC, Piramal Imaging

Matthias Friebe, PhD VP, Radiochemistry Research, Global Drug Discovery, Piramal Imaging

## 1.0 BACKGROUND

NDA 204677 was submitted on December 21, 2012 for Florbetaben F 18 Injection.

Proposed indication(s): 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.

PDUFA goal date: December 21, 2013

FDA issued a Background Package in preparation for this meeting on August 29, 2013. For the purposes of the minutes, the FDA's items are in regular font and the meeting discussion points are indicated in ***bold italics*** below.

## 2.0 DISCUSSION

### 1. Introductory Comments

***Discussion:***

***After introductions, FDA stated the purpose for the Late-Cycle Meeting (LCM) was to share information, discuss the substantive review issues that were identified to date and discuss the objectives for the remainder of the review.***

### 2. Discussion of Substantive Review Issues

#### CLINICAL

- a. We find that the Histopathology study achieved its co-primary efficacy endpoints of regional sensitivity and specificity exceeding the pre-specified thresholds. The study validates the ability of this imaging drug to "stain" amyloid deposits in-vivo, region by region, similarly to where amyloid is found on histopathology (or would be found on autopsy).

The imaging assessments that lead to measurements of sensitivity and specificity were conducted region by region which would not be a practice applicable reading methodology but is acceptable for the conceptual “method validation” purposes. This lack of “practice applicability” also justifies the use of a majority read in these analyses. Notably, the conclusions of the majority read analyses also appear to be confirmed in the reader by reader analyses.

The Standard of Truth here has been determined by the consensus of an off-site central panel of pathologists (CP) who were blinded to the clinical and imaging data but who scored brain sections processed with a variety of stains, including silver stain of neuritic (aka senile) plaques and diffuse (aka amyloid) plaques, and immunohistochemistry of neuritic plaques, diffuse amyloid plaques, and vascular amyloid. Of note, a pathologist counting and scoring neuritic plaques, for example, would also be aware of scoring on other categories in the same specimen.

This scoring method importantly differs from CERAD scoring where amyloid load in a brain section is assessed by only counting neuritic plaques found on silver stain. We note that there were exploratory analyses performed post hoc evaluating imaging performance against different combinations of stains and plaque categories.

- b. We do not accept, as confirmatory, the additional efficacy analyses which were performed in the Histopathology study. Specifically, we do not accept the Standard of Reference (SoR) as defined by on-site histopathology.

The goal of the onsite histopathology evaluation appears to have focused on neurological *disease diagnosis* rather than *amyloid deposition*. Various neurological diseases were evaluated, including Alzheimer’s Disease (AD), Parkinson Disease (PD), , dementia with Lewy Bodies (DLB), multiple system atrophy (MSA), frontal-temporal dementia (FTD). It is not clear how these diseases and various disease stages were ‘collapsed’ to the presence or absence of amyloid deposition for a particular subject.

No protocol was submitted for the methodology used for establishing SoR (presence or absence of amyloid deposition) based on the various neuropathology diagnoses. It is unclear to us how the local pathologists determined the standard of reference for this analysis and whether the pathologists were blinded to clinical data.

The use of local histopathology results as standard of reference has additional limitations:

- There is no clear local histopathology evaluation protocol submitted in the NDA, and it appears from the submission that such a standard protocol/charter for local histopathology evaluation was not developed for the study. Therefore it is unclear if various local sites followed the same procedures and used same criteria in their onsite histopathology evaluation.
- The Central Histopathology Consensus Panel is comprised of a panel of 3 highly qualified neuropathologists, with the Panel’s consensus read as the SOT. The local histopathology evaluation appears to be performed by a single pathologist with unknown qualifications.

Overall onsite histopathology is not acceptable as a standard of truth in providing confirmatory data to demonstrate the effectiveness of Neuraceq.

- c. We are particularly concerned about the results of the Pooled Read study as the only available confirmatory study evaluating the performance of Neuraceq using practice applicable image reading methodology, and the study failed with regard to specificity. We do find that the study was successful in evaluating the reproducibility of image interpretation among five readers (primary efficacy analysis) but note that the readers apparently agreed frequently on an incorrect image interpretation (pre-specified secondary analyses). We are concerned about the high false positive rate and low specificity which becomes lower when the young healthy volunteers are not included in the analysis. The inclusion of young healthy volunteers might artificially inflate specificity results.

We do not understand the reason for the choice of the Standard of Truth in the Pooled Read study and do not know whether it has been pre-specified. It appears that this truth standard was constructed by selecting data from the CP in the Histopathology study. However, instead of limiting such data to assessments of neuritic plaques (as per CERAD), the assessments were based on both neuritic and diffuse plaques.

We do acknowledge that, given the acceptable sensitivity measurements demonstrated in the same study, the Neuraceq imaging, as is, could potentially be used for ruling out the presence of cerebral amyloid, and therefore making a diagnosis of Alzheimer Disease less likely in a given patient. It would still be necessary to define the clinical meaning of being “positive” and “negative” for amyloid based on this study as it has not been defined by CERAD. Even then we note that we so far have only one confirmatory study using practice applicable reading methodology.

- d. Although we acknowledge that low specificity could be related to the small sample size with correspondingly wide confidence intervals around the point estimates of the specificity cohort, we remain concerned that it could also be in part related to the reading methodology. We therefore would like you to consider whether such methodology could be improved resulting in optimization of specificity assessments without sacrificing sensitivity of the test.
- e. We are concerned with data inconsistency between the Histopathology Study and the Pooled Read Study (and between brain regional analysis and subject level analysis). The performance characteristics (sensitivity and specificity) of Neuraceq vary in different studies with different PET reading methodologies, different training processes, and different truth standard. For example, the number of negative cases (by truth standard) among the 31 brains (obtained in Study 14595) is 8 by histopathology consensus panel (CP) in Study 14595, 14 by onsite neuropathological diagnosis in Study 14595, and 10 by CP in Study 16034.
- f. We do not understand the role of “global impression of the scan” in the proposed reading methodology. In describing the recommended methodology, the application states that after evaluating the four pre-specified brain regions the “reader is requested to decide if the results of the interpretation match the global impression of the scan. If not, it is recommended to repeat the systematic visual assessment procedure to ensure

the correctness of interpretation.” Please explain the basis for such a recommendation, how often it would be applied in practice, how many times one should repeat the “visual assessment procedure”, and how one acquires a “global impression of the scan”. The central blinded readers in Study 16034 did not appear to follow the above described reading procedures, and the Case Report Form of Study 16034 does not include any documentation of “global impression of the scan”. Therefore it appears that “global impression of the scan” was not assessed by any pivotal study, and should be considered a new step in a ‘revised reading methodology’ that would need to be validated through another clinical study.

**Discussion-Clinical:**

***FDA stated the Histopathology study achieved its co-primary efficacy endpoints; however the imaging assessments that lead to sensitivity and specificity conducted region by region would not be applicable in real practice, but are accepted as a “method validation.”***

***FDA expressed major concern with the Piramal’s Standard of Truth developed from the evaluation of amyloid load in post-mortem material processed in various manners and evaluated concomitantly by an off-site central panel of pathologists (CP). FDA noted the CP used a variety of stains, however knew the parameters and scoring achieved with each stain. FDA explained that CERAD scoring based on neuritic plaques found on silver stain seems to be the most clinically relevant procedure for assessing amyloid load.***

***FDA discussed concern with the results of the Pooled Read study as the only available confirmatory study failing with regard to specificity. Piramal stated they would provide analyses of data from studies 14595 and 16043, comparing the “practice applicable” PET read data to both CERAD and current histopathology criteria. FDA asked if study 14595 had scans from 32 patients with a truth standard read according to marketing applicable reading methodology and by three blinded readers. Piramal confirmed that for a total of 31 patients the scans were read according to a formal reading methodology for which a reading manual was established. FDA stated the reading manual (Amendment 5) was a late submission that went through multiple revisions. FDA asked if the images were read based on a prospective protocol. Piramal stated that Amendment 5 was developed in 2010. Piramal stated there were separate criteria and a separate reading charter for the regional analyses.***

***FDA explained the Agency will not accept the additional efficacy analyses performed in the Histopathology and Pooled Read study as confirmatory, nor the on-site histopathology as the Standard of Reference.***

***Piramal asked if a new confirmatory study would be needed. FDA suggested that Piramal propose a study based on additional cases with autopsy data from the ongoing histopathology study. Piramal agreed that the assessment of amyloid load based on different Standard of Truth’ were inconsistent.***

Discussion of Substantive Review Issues (cont.)

STATISTICS

- g. It was not possible to reproduce the primary analysis datasets (particularly, the primary endpoint) from the original data source for Study 14595 and 16034. The raw data sets for truth standard determination are not included in the study folders (in NDA submission).
- h. The images in the Pooled Read Study (16034) were selected from various clinical studies, but not all clinical studies of F-18 Florbetaben. Case selection criteria were not clear to us and a selection bias potentially exists.
- i. The data folder for Study A42404 (Study 123456) cannot be found in the submission. The subjects from Study A42404 cannot be found in the ISS data sets.
- j. Study 14595 had 32 autopsy cases (31 assessable and 1 non-assessable). It is unclear to us which one was non-assessable. Based on Module 5 Section 16.2.6 Individual Efficacy Response Data Tabulations for Study 14595, subject 400010011 appears originally nonassessable, but later became assessable based on re-evaluation by the pathology Consensus Panel. Subject 140060004 appears to be assessable for 5 out of 6 brain regions by the pathology Consensus Panel, and was listed among the 32 autopsy cases, but was not included in either the primary efficacy analysis of Study 14595 or subject level sensitivity and specificity evaluation in Study 16034. The above mentioned lack of datasets on truth standard determination makes it almost impossible for us to reproduce and verify the results of various efficacy analyses in Studies 14595 and 16034.

**Discussion- Statistics:**

***FDA explained the difficulty of being unable to locate the raw data sets and reproduce the efficacy analyses for studies 14595 and 16034 (specifically for generating verification of the Standard of Truth from autopsy data). Piramal confirmed that the definitions of the Standard of Truth used in Study 14595 and Study 16034 are different, and agreed to clarify the location of the datasets in the NDA and the programs used for the analyses. FDA agreed to Piramal's proposal for a teleconference to further discuss the outstanding statistical items.***

3. Discussion of Minor Review Issues

**Discussion:**

***See substantive review items above.***

4. Additional Applicant Data:

**Discussion- CMC:**

***Piramal inquired (b) (4). FDA explained that (b) (4) the addition would be normally submitted as a Prior Approval Supplement. The FDA requested Piramal to submit a formal proposal (meeting request) (b) (4) FDA agreed to Piramal's proposal for a teleconference to further discuss review timelines (b) (4)***

5. Information Requests

Chemistry information requests dated August 21 and 23, 2013.

**Discussion:**

***FDA stated Piramal's responses to the requests for information were under review.***

6. Discussion of Advisory Committee Meeting

**Discussion:**

***FDA stated that there were no plans for an Advisory Committee meeting.***

7. REMS or Other Risk Management Actions

**Discussion:**

***FDA stated that there have been no safety concerns/REMS identified in this phase of the review.***

8. Postmarketing Requirements/Postmarketing Commitments

**Discussion:**

***FDA stated that there were no PMCs or PMRs under consideration at this time.***

9. Major Labeling Issues

**Discussion:**

***FDA stated that labeling comments will not be conveyed at this time. FDA explained that there were a number of serious deficiencies in the NDA and the deficiencies need to be resolved before a meaningful labeling discussion could take place.***

10. Review Plans

**Discussion:**

***FDA stated that the remaining review plans consists of completion of consults, tertiary reviews and inspections.***

11. Wrap-up and Action Items

***Piramal proposed new clinical analyses for the histopathology truth standard: Bielschowsky silver stain. FDA concurred and asked Piramal to submit a proposal/justification. FDA stated that the diffuse plaques should not be part of the Standard of Truth.***

12. Information Requests

Chemistry information requests dated August 21 and 23, 2013.

**Discussion:**

***FDA stated Piramal's responses to the requests for information were under review.***

13. Discussion of Advisory Committee Meeting

**Discussion:**

***FDA stated that there were no plans for an Advisory Committee meeting.***

14. REMS or Other Risk Management Actions

**Discussion:**

***FDA stated that there have been no safety concerns/REMS identified in this phase of the review.***

15. Postmarketing Requirements/Postmarketing Commitments

**Discussion:**

***FDA stated that there were no PMCs or PMRs under consideration at this time.***

16. Major Labeling Issues

**Discussion:**

***FDA stated that labeling comments will not be conveyed at this time. FDA explained that there were a number of serious deficiencies in the NDA and the deficiencies need to be resolved before a meaningful labeling discussion could take place.***

17. Review Plans

**Discussion:**

***FDA stated that the remaining review plans consists of completion of consults, tertiary reviews and inspections.***

18. Wrap-up and Action Items

***Piramal proposed new analyses using for the histopathology truth standard Bielschowsky silver stain evaluated by the central panel of pathologists. FDA did not object. FDA asked Piramal to submit a proposal/justification for the use of additional stains. FDA stated that the assessment of diffuse plaques should not be part of the Standard of Truth.***

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/  
-----

LIBERO L MARZELLA  
10/07/2013



NDA 204677

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Piramal Imaging SA  
c/o CBR International Corp.  
Attention: Jeanne M. Novak, PhD  
Authorized U.S. Agent  
2905 Wilderness Place, Suite 202  
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neuraceq (Florbetaben F 18) Solution for Injection 300 MBq.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 10, 2013.  
Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Ms. Sharon Thomas Regulatory Project Manager, at (301) 796-1994.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director (acting)  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** September 10, 2013 at 2:00 PM – 3:30 PM  
**Meeting Location:** FDA, White Oak - Building 22, Conf. Room 1421

**Application Number:** NDA 204677  
**Product Name:** Neuraceq (Florbetaben F 18 Injection)  
**Indication:** Detection of beta amyloid in the brain, thereby assisting in the differential or confirmatory diagnosis in adult patients who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline.  
**Sponsor/Applicant Name:** Piramal Imaging SA

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

## **CLINICAL**

There are two Phase 3 studies submitted with the application – the ‘Histopathology Study’ (Study 14595) and the ‘Pooled Read Study (Study 16034). The Histopathology Study achieved its pre-specified co-primary objectives of assessing sensitivity and specificity based on histopathology as the standard of truth. However the study did not evaluate the product’s sensitivity and specificity in a manner representative of future clinical practice because it used the majority read of 3 readers, conducted analyses on the brain regional level, and used binary PET reading methodology that is not proposed for use in clinical practice. The study therefore does not bear as much clinical significance as the Pooled Read Study, which assesses the product’s performance characteristics using an image interpretation method suitable for clinical practice.

The Pooled Read Study failed to reject the pre-specified combined null hypotheses of sensitivity  $\leq 60\%$  and specificity  $\leq 70\%$  in 3 out of 5 readers, based on histopathology as the standard of truth. Even though the study achieved its pre-specified primary efficacy objective of demonstrating inter-reader agreement by rejecting the null hypothesis of kappa statistic  $\leq 0.6$ , the readers were agreeing on the wrong image interpretation with regard to specificity.

## **STATISTICS**

The statistical results in terms of accuracy (sensitivity and specificity) and reproducibility do not provide enough evidence to support the claims for the detection of  $\beta$ -amyloid in the brain proposed in this NDA. The low specificity (indicating high rate of false positive images) for subjects with autopsy in Study 16034 using practice applicable reading methodology and web-training process should be noted. Agreement on incorrect interpretations suggests an inadequate interpretation method. In addition, the rules for obtaining the subject-level assessment and truth standard are not the same in the two pivotal studies. Particularly, it is not clear how the sponsor determined the truth standard using the consensus histopathology assessment. The performance varies in different studies with different training processes and different approaches for obtaining the subject-level results.

## **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues –65 minutes

Each issue will be introduced by FDA and followed by a discussion.

## **CLINICAL**

- a) We find that the Histopathology study achieved its co-primary efficacy endpoints of regional sensitivity and specificity exceeding the pre-specified thresholds. The study validates the ability of this imaging drug to “stain” amyloid deposits in-vivo, region by region, similarly to where amyloid is found on histopathology (or would be found on autopsy).

The imaging assessments that lead to measurements of sensitivity and specificity were conducted region by region which would not be a practice applicable reading methodology but is acceptable for the conceptual “method validation” purposes. This lack of “practice applicability” also justifies the use of a majority read in these analyses, Notably, the conclusions of the majority read analyses also appear to be confirmed in the reader by reader analyses.

The Standard of Truth here has been determined by the consensus of an off-site central panel of pathologists (CP) who were blinded to the clinical and imaging data but who scored brain sections processed with a variety of stains, including silver stain of neuritic (aka senile) plaques and diffuse (aka amyloid) plaques, and immunohistochemistry of neuritic plaques, diffuse amyloid plaques, and vascular amyloid. Of note, a pathologist counting and scoring neuritic plaques, for example, would also be aware of scoring on other categories in the same specimen.

This scoring method importantly differs from CERAD scoring where amyloid load in a brain section is assessed by only counting neuritic plaques found on silver stain. We note that there were exploratory analyses performed post hoc evaluating imaging performance against different combinations of stains and plaque categories.

- b) We do not accept, as confirmatory, the additional efficacy analyses which were performed in the Histopathology study. Specifically, we do not accept the Standard of Reference (SoR) as defined by on-site histopathology.

The goal of the onsite histopathology evaluation appears to have focused on neurological *disease diagnosis* rather than *amyloid deposition*. Various neurological diseases were evaluated, including Alzheimer's Disease (AD), Parkinson Disease (PD), , dementia with Lewy Bodies (DLB), multiple system atrophy (MSA), frontal-temporal dementia (FTD). It is not clear how these diseases and various disease stages were 'collapsed' to the presence or absence of amyloid deposition for a particular subject.

No protocol was submitted for the methodology used for establishing SoR (presence or absence of amyloid deposition) based on the various neuropathology diagnoses. It is unclear to us how the local pathologists determined the standard of reference for this analysis and whether the pathologists were blinded to clinical data.

The use of local histopathology results as standard of reference has additional limitations:

- There is no clear local histopathology evaluation protocol submitted in the NDA, and it appears from the submission that such a standard protocol/charter for local histopathology evaluation was not developed for the study. Therefore it is unclear if various local sites followed the same procedures and used same criteria in their onsite histopathology evaluation.
- The Central Histopathology Consensus Panel is comprised of a panel of 3 highly qualified neuropathologists, with the Panel's consensus read as the SOT. The local histopathology evaluation appears to be performed by a single pathologist with unknown qualifications.

Overall onsite histopathology is not acceptable as a standard of truth in providing confirmatory data to demonstrate the effectiveness of Neuraceq.

- c) We are particularly concerned about the results of the Pooled Read study as the only available confirmatory study evaluating the performance of Neuraceq using practice applicable image reading methodology, and the study failed with regard to specificity.

We do find that the study was successful in evaluating the reproducibility of image interpretation among five readers (primary efficacy analysis) but note that the readers apparently agreed frequently on an incorrect image interpretation (pre-specified secondary analyses). We are concerned about the high false positive rate and low specificity which becomes lower when the young healthy volunteers are not included in the analysis. The inclusion of young healthy volunteers might artificially inflate specificity results.

We do not understand the reason for the choice of the Standard of Truth in the Pooled Read study and do not know whether it has been pre-specified. It appears that this truth standard was constructed by selecting data from the CP in the Histopathology study.

However, instead of limiting such data to assessments of neuritic plaques (as per CERAD), the assessments were based on both neuritic and diffuse plaques.

We do acknowledge that, given the acceptable sensitivity measurements demonstrated in the same study, the Neuraceq imaging, as is, could potentially be used for ruling out the presence of cerebral amyloid, and therefore making a diagnosis of Alzheimer Disease less likely in a given patient. It would still be necessary to define the clinical meaning of being “positive” and “negative” for amyloid based on this study as it has not been defined by CERAD. Even then we note that we so far have only one confirmatory study using practice applicable reading methodology.

- d) Although we acknowledge that low specificity could be related to the small sample size with correspondingly wide confidence intervals around the point estimates of the specificity cohort, we remain concerned that it could also be in part related to the reading methodology. We therefore would like you to consider whether such methodology could be improved resulting in optimization of specificity assessments without sacrificing sensitivity of the test.
- e) We are concerned with data inconsistency between the Histopathology Study and the Pooled Read Study (and between brain regional analysis and subject level analysis). The performance characteristics (sensitivity and specificity) of Neuraceq vary in different studies with different PET reading methodologies, different training processes, and different truth standard. For example, the number of negative cases (by truth standard) among the 31 brains (obtained in Study 14595) is 8 by histopathology consensus panel (CP) in Study 14595, 14 by onsite neuropathological diagnosis in Study 14595, and 10 by CP in Study 16034.
- f) We do not understand the role of “global impression of the scan” in the proposed reading methodology. In describing the recommended methodology, the application states that after evaluating the four pre-specified brain regions the “reader is requested to decide if the results of the interpretation match the global impression of the scan. If not, it is recommended to repeat the systematic visual assessment procedure to ensure the correctness of interpretation.” Please explain the basis for such a recommendation, how often it would be applied in practice, how many times one should repeat the “visual assessment procedure”, and how one acquires a “global impression of the scan”.

The central blinded readers in Study 16034 did not appear to follow the above described reading procedures, and the Case Report Form of Study 16034 does not include any documentation of “global impression of the scan”. Therefore it appears that “global impression of the scan” was not assessed by any pivotal study, and should be considered a new step in a ‘revised reading methodology’ that would need to be validated through another clinical study.

Discussion of Substantive Review Issues (cont.)

**STATISTICS**

- g) It was not possible to reproduce the primary analysis datasets (particularly, the primary endpoint) from the original data source for Study 14595 and 16034. The raw data sets for truth standard determination are not included in the study folders (in NDA submission).
- h) The images in the Pooled Read Study (16034) were selected from various clinical studies, but not all clinical studies of F-18 Florbetaben. Case selection criteria were not clear to us and a selection bias potentially exists.
- i) The data folder for Study A42404 (Study 123456) cannot be found in the submission. The subjects from Study A42404 cannot be found in the ISS data sets.
- j) Study 14595 had 32 autopsy cases (31 assessable and 1 non-assessable). It is unclear to us which one was non-assessable. Based on Module 5 Section 16.2.6 Individual Efficacy Response Data Tabulations for Study 14595, subject 400010011 appears originally non-assessable, but later became assessable based on re-evaluation by the pathology Consensus Panel. Subject 140060004 appears to be assessable for 5 out of 6 brain regions by the pathology Consensus Panel, and was listed among the 32 autopsy cases, but was not included in either the primary efficacy analysis of Study 14595 or subject level sensitivity and specificity evaluation in Study 16034. The above mentioned lack of datasets on truth standard determination makes it almost impossible for us to reproduce and verify the results of various efficacy analyses in Studies 14595 and 16034.

3. Information Requests – 10 minutes

- Chemistry information requests dated August 21 and 23, 2013.

4. Postmarketing Requirements/Postmarketing Commitments

- There are no Post Marketing Requirements or Post Marketing Commitments under consideration at this time.

5. Review Plans – 5 minutes

- Completion of consults and tertiary reviews.
- Completion of inspections.

6. Wrap-up and Action Items – 5 minutes

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

/s/  
-----

LIBERO L MARZELLA  
08/29/2013