

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204677Orig1s000**

**OFFICE DIRECTOR MEMO**

## Office Director Decisional Memo

<b>Date</b>	March 19, 2014
<b>From</b>	Sandra L. Kweder, MD, FACP
<b>Subject</b>	Office Director Decisional Memo
<b>NDA/BLA #</b>	204667
<b>Applicant Name</b>	Piramel Imaging
<b>Date of Submission</b>	12/21/2012
<b>PDUFA Goal Date</b>	3/21/2014
<b>Proprietary Name / Established (USAN) Name</b>	Neuraceq Florbetaben F18
<b>Dosage Forms / Strength</b>	Solution for Injection/ 50 to 5000 MBq per mL at calibration time
<b>Proposed Indication(s)</b>	For Positron Emission Tomography (PET) imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline
<b>Action:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Brenda Ye, M.D.
Statistical Review	Lan Huang, PhD
Pharmacology Toxicology Review	Sunny Awe, PhD
CMC Review/OBP Review	Ann Marie Russell, PhD
Microbiology Review	Erika Pfeiler, PhD
Clinical Pharmacology Review	Christy John, PhD
OPDP	Emily Baker
OSI	Lee Jong Hoon, MD
CDTL Review	Alex Gorovets, MD
OSE/DMEPA	Kevin Wright, PharmD
OSE/DRISK	Amarylis Vega, MD

OND=Office of New Drugs  
 OPDP=Office of Prescription Drug Promotion  
 OSI= Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management

## I. Introduction and Background

Alzheimer's disease is a growing public health problem in western countries and the subject of a much basic and clinical research related to prevention and treatment. A critical aspect of any such research relies on diagnosing the condition through a combination of clinical signs and symptoms and radiologic testing as brain histopathology to detect extracellular B-amyloid deposits in the brain neither practical nor acceptable. In recent years positron emission tomography (PET) has increasingly been relied on as a tool for diagnosis, particularly using F18 radiolabeled nuclid3es which are known to have high degrees of affinity for binding amyloid deposits. Two products are approved for such use, florbetapir (Amyvid) and flutemetamol (Vizamyl). This NDA is for florbetaben (Neuraceq), is the 3<sup>rd</sup> application for an F18 amyloid imaging agent for use with PET. The original goal date was December 21, 2013, but based on deficiencies noted at the Late Cycle Meeting, the sponsor developed and completed an additional clinical study, submitting it as a Major Amendment.

I concur with the recommendation in Dr. Marzella's Division Director review that this NDA should be approved for marketing. Overall, the data submitted by the applicant support the conclusion that florbetaben F18 is safe and effective for use with PET as a tool in assessing patients with cognitive impairment, as is described in the agreed labeling between the division and the sponsor. A negative scan is indicative of sparse to no neuritic plaques and is thereby inconsistent with a diagnosis of Alzheimer's disease (AD). A positive scan indicates moderate to frequent amyloid neuritic plaques, which are often indicative of AD, but may also be present in patients with other types of neurologic conditions, as well as older patients with normal cognition.

Critical milestones in the regulatory science underlying assessment of amyloid imaging include the following:

- **2008 FDA Advisory Committee Meeting** – assessed the clinical utility of amyloid imaging by PET. The committee recommended that, because many well elderly are known to have amyloid deposits in the brain, amyloid imaging's key role would be in ruling out the diagnosis of Alzheimer's disease. In other words, a negative scan for amyloid scan is helpful to confirm that Alzheimer's Dementia (AD) is not present. This makes the specificity (and negative predictive value) of a diagnostic test important.
- **2011 FDA Advisory Committee Meeting** – as part of its review of a different F18 agent the committee discussed reading methodology and training of readers. They stressed the importance of training tools so that multiple readers can be trained using a web-based system and able to reach the same determination of a positive or negative amyloid scan across a variety of images from patients with different final diagnoses.
- **2012 NDA 20-2008 AMYVID (florbetapir F18 injection) approval** – Key efficacy results included:

- Performance characteristics (sensitivity and specificity) by trained readers, with histopathology as a standard of truth (SOT). For autopsied patients, 5 readers who were trained by electronic methods found Amyvid to have a median of 82% sensitivity (Range 69 - 92) and median specificity 95% (range 90 - 95).
- Agreement (kappa statistic) among 5 readers in a second study were 0.83 (95% CI: 0.78 to 0.88) for 151 images in the primary data set (meeting the primary endpoint of a lower bound of the 95% CI being > 0.58). Secondary endpoints in this study determined that the reproducibility of the reads was similar for patients with and without histopathology.
- **2013 NDA 20-3137 VIZAMYL( flutemetamol F18 injection) approval** - Key efficacy results included:
  - Performance characteristics (sensitivity and specificity) by trained readers, with histopathology as SOT. For the autopsied patients, five readers showed 93% median sensitivity (range 86-93) and 84% specificity (range 60-92).
  - In a second, larger pooled study, inter-reader reproducibility analysis showed an overall kappa statistic of 0.83 (95% CI 0.79 to 0.86) which met the pre-specified success criterion (95% CI lower bound >0.60).

Key Aspects of this NDA for Neuraceq are summarized below.

## II. Safety Considerations

The clinical reviews reflect that the safety and tolerance properties of Neuraceq among 900 exposed patients are highly similar to other F18 injection products for use with PET, all of which are for single dose administration. The most common reported adverse events at the proposed dose are focal and transient pain at the injection site and mild to moderate headache in the first hour after injection, which resolve.

## III. Efficacy and Performance

The original NDA submissions highlighted two studies in support of efficacy, much like those of previous F18 imaging agents.

**Study #14595** - first was a histopathology study of over 200 patients with cognitive impairment who had short life-expectancies who underwent florbetaben PET scan. The primary analysis of the 31 patients who died and had autopsy brain pathology testing for amyloid established the cohort for the histopathology standard of truth (SOT). Methods for brain sampling and staining, as well as slide reading are described in the clinical and CDTL reviews, among others. PET scans of six different brain regions for each of the 31 patients were read by three independent, blinded readers using an algorithm that sought to ascertain regional sensitivity and specificity. The study met its primary objective. Blinded readers

were able to reliably assess regional amyloid burden with sensitivity of 77% (range 66-89) and specificity of 94% (range 89-100). Secondary endpoints were also confirmed, including assessing reliability of a global scan results, which is more applicable to how the agent will be used in practice. For this aspect of the trial a new set of blinded readers were employed. One of the criticisms of Study #14595 was that the readers were not trained using electronic or web-based systems, which is what will be used by most practitioners. However, this is essentially a proof of concept study and I find the method reasonable for this purpose.

**Study #16043** - The second phase study was based on 454 brain scans obtained from a variety of smaller studies that included a mix of patients with various types of cognitive impairment and dementia, as well as some normal volunteers. It was a “pooled read” study that employed five independent image readers who had been trained using an electronic training tool (more clinically relevant to standard practice). The purpose of this study was to assess inter-reader reproducibility, overall and according to type of subject (those with and without histopathology; those with AD and those with mild cognitive impairment). The overall kappa statistic for agreement was 0.80 (95% CI 0.77, 0.83), which met the primary goal for the study. Agreement among 5 of 5 readers across all groups of patient types was similarly high, ranging from 75% to 83%.

Of note, a secondary objective of this pooled study was to establish accuracy and it did not meet this test. The study met its sensitivity threshold ranging among the readers from 78% to 90% with lower bound of the 95% CI ranging from 62% to 76% (the pre-specified threshold for the lower bound was 60%). It did not meet its endpoint of specificity. When one removed the healthy normal volunteer subjects from the analysis, the point estimates for sensitivity across the five readers ranged from 64% to 86%. Of particular concern was the fact that the lower bound of the 95% CI for these results were 42%, 35%, 42%, 35% and 57%, which the review team found very concerning. The key issue with inclusion of healthy volunteer subjects is that their imaging results have key anatomic differences that are likely to signal to readers that no amyloid is present and thereby bias results when they are included. It was on the basis of these data that the review team raised concerns at the Late Cycle Meeting with the sponsor, resulting in a confirmatory study.

**Confirmatory Study (Expanded 14595)** - The third study, submitted as a major amendment to the NDA, was conducted to confirm accuracy of florbetaben F18 PET imaging by a protocol in which all images obtained from the original histopathology study for which brain autopsy pathology tissue was available. By the time this study was conducted additional patients from the study had died and brain histopathology was available for 82 subjects. Five blinded independent readers, this time trained using a web-based practice-relevant system, resulted in more favorable findings. For each of the readers the lower bound of the 95% CI for sensitivity was >70% (the pre-specified threshold was that three of the five readers must have a lower bound of > 60%). For specificity, three of the five readers were required to have a lower bound of the 95% CI for specificity above 50%. The study met this threshold, as well. .

### Related Considerations

Subgroup analyses in a clinical trial program such as this are challenging to conduct, because the size of the population serving as the SOT is quite small. Thus, to assess whether there are differences in the performance of florbetaben F18 by sex, ethnicity, age or other demographics with statistical certainty

would require one to increase the postmortem sample size substantially. However, the assessments conducted by the sponsor and reviewed by the Division are reassuring that there are not likely to be differences in utility of florbetaben in men versus women, among different race and ethnic groups or by patient age. For example, for the five readers in the third study, sensitivity values for male patients were 97-100% and for female patients 83-100%. Specificity values were 33-78% for male patients and 67-92% for females. Of the 978 patients who comprised the safety database, 46% were female, so certainly well representative of the population of individuals who may be exposed to the drug, and there was no imbalance in adverse events. With regard to race or ethnicity, the majority of patients in the safety database were Caucasian (nearly 84%) and Asian (13%), which is explained by the fact that 75% of patients exposed were from Europe, Australia and Japan, with the remainder from the United States. Only 1.7% of patients were Black; while this is extremely disappointing, there is no reason to expect differences in adverse events by race or ethnicity for this single use drug. Finally, analyses by age are somewhat less relevant in this application than in other therapeutic areas, because most of the patients are beyond middle age. It is one of the reasons that inclusion of young, healthy volunteers in the studies is considered by some to potentially bias results of test characteristics.

Previous applications for F18 PET imaging agents have necessarily addressed how readers in the clinical studies were trained as it is essential that results be relevant to how the product will be used in clinical practice. As noted above this was a topic discussed in detail by an FDA advisory committee. These issues were taken into account in planning for this NDA and relevant results for readers trained using web-based programs were those focused on in the reviews.

#### IV. Other Aspects of Review

There are no outstanding regulatory issues for this NDA. Pediatric studies have been appropriately waived. No postmarketing studies or clinical trials commitments or requirements are needed, nor is a risk and evaluation and mitigation strategy.

#### V. Conclusion

Florbetaben F18 injection (Neuraceq) should be approved as a new imaging agent for estimation of amyloid neuritic plaques in the brain.

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SANDRA L KWEDER  
03/19/2014