

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202008Orig1s000

OTHER REVIEW(S)

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

Label and Labeling Review

Date: March 6, 2012

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

Team Leader Todd Bridges, R.Ph.
Division of Medication Error Prevention and Analysis

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

Drug Name: Amyvid (Florbetapir F 18 Injection)
37 MBq/mL to 1900 MBq/mL (1 mCi/mL to 50 mCi/mL)

Application Type/Number: NDA 202008

Applicant: Avid Radiopharmaceuticals

OSE RCM #: 2011-3994

1 INTRODUCTION

This review evaluates the bulk drug product shield and vial labels received on October 7, 2011, for Amyvid (Florbetapir F 18) Injection in response to a request from the Division of Medical Imaging Products (DMIP).

1.1 PRODUCT INFORMATION



The recommended single intravenous bolus dose for Amyvid is 370 MBq (10 mCi) in a dose volume of less than or equal to 10 mL. Amyvid is supplied in 10 mL, 10-30 mL, and 10-50 mL multi-dose vials. Each vial is packaged in a shielded container of appropriate thickness to minimize external radiation exposure. Amyvid should be stored at 25°C (77°F); excursions are permitted from 15° to 30° C (59°-86° F).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following labels:

- Bulk Drug Product Shield Labeling submitted on October 7, 2011, see Appendix A
- Bulk Drug Product Vial Label submitted October 7, 2011, see Appendix B
- Prescribing Information submitted October 7, 2011 (no image)

This review focuses on the labels and labeling submitted on October 7, 2011. Our analysis considered the distribution system for radioactive pharmaceuticals, the site of production preparation and the use of multi-dose vials.

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

3 RESULTS

3.1 MULTI-DOSE VIAL PACKAGE CONFIGURATIONS

Our analysis of the labels and labeling considered the distribution system for radioactive pharmaceuticals, the site of product preparation, and the appropriateness of multi-dose vials for this product. The distribution system for radiopharmaceuticals is more restrictive from that of non-radioactive pharmaceutical distribution system. Amyvid is supplied as a radioactive pharmaceutical from the manufacturer. This differs from other radiopharmaceuticals in that activation does not occur at the nuclear pharmacy. The distribution of Amyvid will be limited to nuclear pharmacies since the product will be shipped radioactive from the applicant. Upon receiving the product nuclear pharmacies calibrate the solution to prepare the dose, 370 mBq, of Amyvid to dispense to the end user. Amyvid has a relatively short half life, 110 minutes. The use of multi-dose vials would allow the manufacturer to provide a 24-hour window for dose preparation for multiple doses. Additionally, the use of multi-dose vials has been employed in other radiopharmaceuticals such Chromitope Sodium and Isojex. In summary, multi-dose vials are an acceptable package configuration for this product.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors. We recommend the following revisions below be implemented prior to approval:

4.1 COMMENTS TO THE DIVISION

Our review of the insert labeling noted where information can be clarified and improved upon to minimize the potential for medication errors.

Insert Labeling

- 1) Delete all trailing zeroes that appear throughout the insert labeling. Trailing zeroes (e.g. '1.0') are considered dangerous abbreviations². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.
- 2) Revise the proposed proprietary name throughout the labeling to title case (i.e., Amyvid). We noted currently "AMYViD" utilizes mixed case lettering (e.g. tall man lettering) in the insert labeling. For example, "AMYViD" appears in all capital letters with the exception of the "i" which appears in lower case. Tall man lettering is reserved for look-alike medications that are commonly confused. Therefore, we request that the Division revise the presentation of the name.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 01/03/2012.

4.2 COMMENTS TO THE APPLICANT

Our review of the shield labeling and vial label identified the following deficiencies:

Bulk Drug Product Vial Label and Shield Labeling

- 1) Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
- 2) Revise the proposed proprietary name throughout the label and labeling to title case (i.e., Amyvid).
- 3) Delete all trailing zeroes throughout the label and labeling.
- 4) Ensure the statement on product storage includes the permitted temperature excursions, 15° C to 30° C (59° F to 86° F), from the insert labeling.
- 5) Relocate: “Caution: Radioactive Material” to follow radioactive warning symbol.
- 6) Revise the statement (b) (4) to read “For Intravenous Use”, and increase the prominence of this statement.
- 7) Ensure the finished package form bears conspicuously the name and place of business of the manufacturer and distributor in accordance to 21 CFR 201.1(b)(1).

If you have further questions or need clarifications, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

APPENDICES

Appendix A: Proposed Bulk Drug Product Shield Labeling

Bulk Drug Product Shield Label



Appendix B: Proposed Bulk Drug Product Vial Label

Bulk Drug Product Vial Label



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/s/

KEVIN WRIGHT
03/06/2012

TODD D BRIDGES
03/06/2012

CAROL A HOLQUIST
03/06/2012

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

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

Memorandum

Date: 2/27/2012

To: Sharon Thomas, Regulatory Project Manager
Division of Medical Imaging Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 202008,
Amyvid (florbetapir F 18)

In response to your labeling consult request on October 14, 2011, we have reviewed the draft Package Insert for Amyvid and offer the following comments. Note that these comments are based upon the February 22, 2012 version of the label.

Section	Statement	Comment
5.1 Risk for Image Misinterpretation	(b) (4)	(b) (4)
5.1 Risk for Image Misinterpretation	(b) (4)	We recommend removing this statement from the PI. It implies that (b) (4)

	(b) (4)	(b) (4), when this is not always the case. In addition, (b) (4) is not substantial to include in the PI.
14 Clinical Studies	Table 8 59 autopsy 92 non-autopsy	The values for (b) (4) for these two categories are displayed as (b) (4). We are not sure if these are placeholders for values to be inserted or if these columns are not applicable. We recommend inserting the correct values or replacing the (b) (4) with (b) (4) and describe why in a footnote.
14 Clinical Studies	Table 8 49 AD 57 MCI 20 cognitively normal elderly 12 end of life, with normal cognition 13 other dementia disorder	This table displays results for subgroups of patients with various clinical diagnoses. According to the other sections of the PI, Amyvid efficacy has not been established as a diagnostic or predictive tool. In addition, image interpretation is performed independently of a patient's clinical features. Therefore, data presented on subgroups of patients with clinically determined diagnosis, is misleading. Patients image interpretation and results are evaluated independent from their diagnosis. We recommend removing the subgroups from the chart and leaving just the autopsy and non-autopsy rows and a total.

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/s/

JAMES S DVORSKY
02/27/2012



Pediatric and Maternal Health Staff
Office of New Drugs
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Silver Spring, MD 20993
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Maternal Health Team Review

Date: February 24, 2012 **Date Consulted:** October 20, 2011

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Drug: Amyvid (florbetapir F 18) NDA 202008

Subject: NDA resubmission, Pregnancy and Nursing Mothers Labeling

Sponsor: Avid Radiopharmaceuticals, Inc.

Materials Reviewed: Amyvid (florbetapir F 18) product labeling

Consult Question: The division requested assistance in the review of the proposed PI for NDA 202-008 as it relates to pregnancy and lactation.

INTRODUCTION

Avid Radiopharmaceuticals, Inc. (Avid) submitted a New Drug Application, NDA 202-008 for Amyvid (florbetapir F 18) Injection on September 17, 2010 with the proposed indication for use as a diagnostic radiopharmaceutical for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β -amyloid, a defining pathology of Alzheimer's disease (AD), which is the most common type of dementia (50-70%). Avid was granted a priority review and on October 4, 2010 the Division of Medical Imaging Products (DMIP) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) to review the Amyvid proposed label as it relates to pregnancy and lactation. MHT provided labeling recommendations in a review dated January 18, 2011. DMIP completed a review of the application and issued a complete response (CR) letter on March 17, 2011 citing clinical, product quality, labeling and facilities inspection deficiencies. MHT labeling recommendations were not conveyed to the sponsor in the March 17, 2011 CR communication. On October 7, 2011 the sponsor submitted a NDA resubmission in response to the division's CR letter and DMIP consulted MHT on October 20, 2011 for assistance in reviewing the sponsor's proposed labeling as it relates to pregnancy and lactation.

BACKGROUND

Alzheimer's Disease

Alzheimer's disease (AD) is an irreversible, progressive brain disease that slowly destroys memory and cognitive functioning, eventually leading to the inability to carry out simple tasks, including activities of daily living. It is the most common form of dementia in older people, with symptoms first appearing after age 60. It is estimated that approximately 5.1 million Americans may have Alzheimer's disease, for which there is no cure¹. Changes in the Alzheimer's brain occur over a long period of time and damage to brain cells or neurons appear in two forms:

- Beta-amyloid (β -amyloid) Plaques: clumps of protein that may interfere with communication between brain cells.
- Tau Protein Tangles: Tau is a protein that normally occurs in threads in the brain to support normal brain function. In the Alzheimer's brain, tau protein threads undergo alteration that causes them to become tangled. These tangles are thought to cause serious damage to neurons².

Diagnosis of AD usually occurs by ruling out other causes of symptoms via a series of laboratory tests, neuropsychological testing and brain imaging. Positron emission tomography (PET) is one type of imaging used to detect less active areas of the brain and density of amyloid plaques. Although there are diagnostic tests and imaging to rule out other causes and symptoms similar to those in Alzheimer's patients, there is currently no diagnostic test to positively identify changes associated with Alzheimer's disease. Currently, Alzheimer's disease can only be confirmed by post-mortem examination of the brain³.

¹ Website: <http://www.nia.nih.gov/Alzheimers/Publications/adfact.htm>. National Institute on Aging, National Institutes of Health.

² Website: <http://mayoclinic.com/health/alzheimers-disease/DS00161>. Mayo Foundation for Medical Education and Research (MFMER). January 17, 2009.

³ Website: <http://mayoclinic.com/health/alzheimers-disease/DS00161>. Mayo Foundation for Medical Education and Research (MFMER). January 17, 2009.

Radiopharmaceutical Use in Pregnancy and Lactation

Diagnostic procedures utilizing radiopharmaceuticals may become medically necessary for women during pregnancy or lactation. Exposure of an embryo, fetus or nursing child to radiopharmaceuticals may result from placental transfer, exposure to maternal tissues (breast or bladder) or via breast milk after maternal radionuclide administration⁴. The potential for fetal harm depends on the fetal gestational age and the dose of radiation received⁵. For lactating women, interrupting breast feeding for a period of time may be necessary with some diagnostic radiopharmaceuticals⁶. When diagnostic procedures with radiopharmaceuticals become medically necessary, for pregnant or lactating women, efforts should be exercised to reasonably minimize exposure of the women and subsequent fetal or infant exposure⁷.

This review provides MHT recommended revisions to the highlights, pregnancy and nursing mothers sections of the sponsor's proposed labeling.

REVIEW OF SUBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling (see Appendix A)

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

There are no animal reproductive toxicology data for Amyvid. Based on the FDA Guidance "Medical Imaging of Drug and Biologic Products Part I: Conducting Safety Assessments", Avid requested and FDA granted a waiver of reproductive toxicology studies, as the intended population for florbetapir F 18 is patients with Alzheimer's disease, who are primarily elderly males and post-menopausal females.

The MHT acknowledges that the use of Amyvid in pregnant or lactating women will be most likely rare, as the diagnostic indication for Amyvid (imaging of β -amyloid plaques, a pathology of Alzheimer's Disease) is rare among females of reproductive potential. However, adequate use information for all radiopharmaceuticals should be available for females of reproductive potential to better inform labeling and clinical decision making when such imaging is needed. Labeling sections were revised to accommodate the appropriate required regulatory language. In addition, the PMHS maternal health team

⁴ Website: http://rpop.iaea.org/RPOP/RPop/Content/SpecialGroups/1_PregnantWomen/index.htm. International Atomic Energy Agency, 2010.

⁵ Website: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/Pregnancy.aspx. American College of Radiology, 2008.

⁶ Website: <http://hps.org/physicians/>. Health Physics Society, December 2009.

⁷ Website: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/Pregnancy.aspx. American College of Radiology, 2008.

suggests adding language to the pregnancy subsection of labeling about determining the pregnancy status of females of reproductive potential prior to exposure to Amyvid.

The United States Nuclear Regulatory Commission provides specific guidelines regarding periods of breast feeding cessation for some radiopharmaceuticals. Although there is no specific guideline regarding breast feeding cessation for lactating women exposed to F 18 containing radiopharmaceuticals, it is reasonable to provide information regarding pumping and discarding breast milk for consideration of the healthcare professional and the patient.

PMHS-MHT labeling recommendations (label excerpts) appear below. Appendix B of this review provides a tracked-changes version of labeling that highlights the recommended PMHS-MHT revisions.

MHT Labeling Recommendations (label excerpts):

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. It is not known whether AMYViD can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted with AMYViD. AMYViD should be administered to a pregnant woman only if clearly needed.

All radiopharmaceuticals, including AMYViD, have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the magnitude of the radiopharmaceutical dose. Assess pregnancy status before administering AMYViD to a female of reproductive potential.

8.3 Nursing Mothers

It is not known whether AMYViD is excreted in human milk. Because many drugs are excreted into human milk and because of the potential for radiation exposure to nursing infants from AMYViD, temporarily interrupt breastfeeding for 24 hours (>10 half-lives of radioactive decay for the F 18 isotope) after exposure to AMYViD. If breastfeeding is interrupted, the patient should pump and discard her breast milk and use alternate infant nutrition sources (e.g., stored breast milk or infant formula) for 24 hours after administration of the drug.

7

Appendix A- Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

(b) (4)

AMYViD should be administered to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

(b) (4)

Appendix B-MHT Tracked Changes Labeling Revisions

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/s/

TAMMIE B BRENT HOWARD
02/24/2012

MELISSA S TASSINARI
02/24/2012

LISA L MATHIS
02/28/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 19, 2012

TO: Sharon Thomas, Regulatory Project Manager
Qi Feng, Medical Officer
Division of Medical Imaging Products

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

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

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 202-008

APPLICANT: Avid Radiopharmaceuticals, Inc.

DRUG: Amyvid[®] (florbetapir F-18) Injection

NME: Yes

INDICATION: Evaluation of Alzheimer's disease

REVIEW CLASSIFICATION: Priority, Class 2 Resubmission

CONSULTATION REQUEST DATE: November 10, 2011

INSPECTION SUMMARY GOAL DATE: February 7, 2012

DMIP ACTION GOAL DATE: March 28, 2012

PDUFA DUE DATE: April 7, 2012

I. Background

Avid Radiopharmaceuticals, Inc. resubmitted this application as a Class 2 Resubmission for the use of Amyvid® (florbetapir F-18) in the evaluation of Alzheimer's disease (AD).

AD is the most common cause of dementia in the elderly, affecting more than four million people in the United States alone (1% prevalence). Most AD cases occur sporadically, but rare familial mutations are known to be genetically inherited (typically autosomal dominant). Mild cognitive impairment (MCI), an intermediate stage between the expected cognitive decline of normal aging and dementia, appears to be a risk factor for developing AD.

Although the etiology remains unknown, the amyloid-beta (A β) peptide appears to be important to the pathogenesis of AD. Transgenic mice with one or more of the mutant human genes develop amyloid plaques and show behavioral deficits that parallel those of AD patients. Experimental therapies that reduce the A β peptide burden (decrease production and/or increase clearance) have been successful in reversing the behavioral deficits in affected mice, and some of these therapies are beginning to be investigated in clinical trials.

Accumulation of A β -fibrils (amyloid plaques) is a key histopathologic criterion at autopsy confirmation of AD. Currently, the diagnosis often proves incorrect at autopsy, even when consensus clinical diagnostic criteria had been rigorously applied. In the search for a clinically useful biomarker, florbetapir F-18 has been identified as a novel imaging agent for use in positron emission tomography (PET), as a potential clinical biomarker of choice in diagnosing AD. Preclinical studies to date have shown that florbetapir F-18 exhibits specific and sensitive binding to amyloid plaques, the currently recognized hallmark of AD.

Study Medication

The sponsor (Avid Pharmaceuticals, Inc.) has developed a novel florbetapir F-18 PET imaging method which includes, as an integral component of the method, a user training program for interpreting the images obtained. The imaging method (including the training program) has been tested in three clinical studies, and the overall study results generally supported clinical utility. However, the need for detailed in-person user training is expected to limit the applicability of the imaging method in clinical practice: user training is difficult to standardize, validate, and efficiently implement widely. To support the clinical applicability of the imaging method, the sponsor has developed an automated web-based user training program as the standardized program for efficient implementation, and conducted Study ¹⁸F-AV-45-PT01 to validate the automated program.

Study ¹⁸F-AV-45-PT01

This training study was designed and conducted "on-line" by [REDACTED] (b) (4), a contract research organization (CRO). Five nuclear medicine physician trainees naive to the florbetapir-PET method completed the automated web-based training program and then interpreted images collected from 151 subjects in two previously completed florbetapir F-18 studies. The "subjects" for this training study were the five physician trainees: no patient subjects were enrolled and no study drug was administered.

Each reader completed the web-based training program at the reader's institution, independently from each other, without external input, and using the reader's own computer equipment. Following completion of training, the readers continued to work independently to interpret the images obtained in two prior Studies ¹⁸F-AV-45-A05 and ¹⁸F-AV-45-A07 using a standard nuclear medicine viewer system. All images were blinded with respect to demographic and clinical data, and to the presence repeat scans.

- *Primary Objective:* To validate a web-based training program for educating nuclear medicine and radiology physicians in interpreting florbetapir-PET scans in the clinical setting.
 - A statistical assessment of the *inter-reader agreement* was to be used as the measure of successful validation: Fleiss's kappa statistic > 0.64 (lower bound of the 95% confidence interval > 0.58). The sponsor presents results that support a statistic of about 90%.

- As an additional measure of robustness, *intra-reader reproducibility* was qualitatively assessed using blinded re-interpretations of 33 randomly selected images. The sponsor presents results that support an intra-reader reproducibility approaching 95%.
- *Secondary Objective:* To characterize the performance characteristics of the florbetapir PET method: reader-specific (and mean) sensitivity and specificity. Under the current study, the florbetapir-PET method has been redefined to include a validated automated web-based training program, making it possible to determine the method's performance characteristics.
- *Training Program:* The read methodology requires the reader to systematically review the images and interpret the scans as positive if there are: (1) at least two brain regions with loss of gray-white contrast, OR (2) at least one region with intense gray matter uptake. The web-based training material consisted of the following:
 - Introduction to Alzheimer's disease pathology
 - Description of the binary read methodology
 - Scan evaluation procedures and interpretation criteria
 - 12 practice florbetapir-PET scans with structured discussion of the the correct interpretation
 - 20 practice florbetapir-PET scans with with answer key for self-assessment
- *Program Validation:* The contract research organization (CRO) (b) (4) set up the database to capture the reader's scan interpretation results, designed the electronic case report form (eCRF), and provided the readers with unique login passwords for data entry.

A total of 151 unique florbetapir-PET image sets and 33 repeat sets (total 184) were grouped into 6 batches. The repeat images and their originals were deliberately not grouped into the same batch. The interpretation results of only one batch could be submitted on any given day and only in sequential batch order. Each reader rated each image as either positive or negative for significant tracer accumulation in cortical gray matter. The reader also indicated their confidence level (low, medium, high), as well as all scan features that contributed to any reduced confidence. The images used in validating the training program were selected as follows:

139 primary image sets (batches 1 - 4):

- 60 sets from Study ¹⁸F-AV-45-A05 (20 controls, 20 MCI, and 20 AD)
- 59 sets from ¹⁸F-AV-45-A07 (brain autopsy results available)
- 20 randomly selected duplicates of the 60 sets from Study ¹⁸F-AV-45-A05

45 additional image sets (batches 5 and 6):

- 32 sets from Study ¹⁸F-AV-45-A05 (all from MCI patients)
- 13 randomly selected duplicates of the 32 sets from Study ¹⁸F-AV-45-A05

- *Performance Characteristics Evaluation:* In conjunction with the "truth standard" data from prior studies, the image interpretation results were analyzed to establish the sensitivity and the specificity of the florbetapir PET method in diagnosing AD. The sponsor reports sensitivity and specificity results of 85% and 95%, respectively.

The results of this Study ¹⁸F-AV-45-PT01 are currently under review at CDER as a second cycle review of a Class 2 Resubmission of NDA 202-008. The proposed indication for use statement reads as follows:

(b) (4)

II. INSPECTION RESULTS

Original Review Cycle

Three good clinical practice (GCP) inspections revealed no significant GCP deficiencies (no actions indicated, NAI), as shown below. Details of the inspectional findings are summarized in *Clinical Inspection Summary* for NDA 202-008, dated January 19, 2011.

Three Inspections of Study 18F-AV-45-A07

Inspected Entity	Site (Subjects)	Inspection Dates	Outcome Classification
Adam Fleisher, M.D.	Site 145 (N = 20)	Dec 6 - 13, 2010	NAI
Ralph Coleman, M.D.	Site 217 (N = 25)	Nov 15 - 22, 2010	NAI
Avid Pharmaceuticals, Inc.	Sponsor	Jan 3 - 7, 2011	NAI

Current Review Cycle, Class 2 Resubmission

(b) (4) was inspected as the CRO, and the sole entity, that conducted Study 18F-AV-45-PT01 (no clinical investigator sites) to validate the automated user training program. The inspectional findings are summarized below.

Inspection of (b) (4): Study 18F-AV-45-A07

Inspected Entity (CRO)	Study	Inspection Dates	Outcome Classification
(b) (4)	18F-AV-45-PT01	Jan 3 - 4, 2012	Pending (Preliminary NAI)

NAI = no deviation from regulations

VAI = deviation from regulations

OAI = significant deviation from regulations and/or data unreliable

Pending: This preliminary outcome classification is based on information on Form FDA 483 and communication with the field investigator; final establishment inspection report (EIR) has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary (CIS).

Inspection of CRO (b) (4)

- a. What was inspected:
- Scope of inspection:
 - Adherence to contractual agreement with the sponsor
 - Adherence to applicable GCP regulations
 - Adherence to study protocol
 - Verification of efficacy data
 - Efficacy data verification:
 - Qualitative amyloid burden, including *Analysis Dataset Reader Training* (ADRT) data listing
 - Confidence level assessment
 - Test-retest correlation
- b. General observations and commentary:
- No deficiencies were observed and a Form FDA 483 was not issued. The CRO adhered to the study protocol, contractual agreement with the sponsor, and all applicable GCP regulations.
 - The efficacy data reported in the NDA were compared against the corresponding data on eCRFs. No discrepancies were noted.
 - There was no evidence of reader unblinding or other biases in interpreting images or reporting interpretation results. The database controls appeared adequate in preventing data entry errors and in tracking changes to existing data.
 - Reader name, image interpretation outcome (amyloid burden), and subject identification information shown on the ADRT data listing (provided by DMIP with original consult request) matched those in the corresponding eCRFs.
- c. Assessment of data integrity: The efficacy data from this CRO site appear reliable.

Observations noted above for the CRO inspection site are based on Form FDA 483 and preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In support of this second cycle NDA review, the conduct of Study ¹⁸F-AV-45-PT01 by the CRO (b) (4) was inspected. No deficiencies were observed and a Form FDA 483 was not issued. The study appeared to have been conducted in accordance with the study protocol, contractual agreement with the sponsor, and applicable GCP regulations.

Study ¹⁸F-AV-45-PT01 was designed and conducted by the sponsor's CRO (b) (4) to validate the effectiveness of a self-administered, web-based PET image interpretation training program. The sponsor intends to incorporate the reader training program into the PET imaging method, as an integral component of the imaging method. In inspecting the CRO's conduct of Study ¹⁸F-AV-45-PT01, a major specific aim was to verify the ADRT data listing (reader training testing results), a key component of reader training program validation. The results shown on the ADRT and other related efficacy data listings appeared reliable as reported in the NDA.

Note:

The final EIR has not been received from the field office and the final classification of the inspection outcome remains pending. The observations noted above are based on preliminary communications with

the field investigator. An addendum to this inspection summary will be forwarded to the review division if any final classification changes from the pending classification, or if additional observations of clinical or regulatory significance are discovered after completing the EIR review.

{See appended electronic signature page}

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INTRODUCTION

On October 7, Avid Radiopharmaceuticals submitted a Complete Response submission for Amyvid (florbetapir F 18) Injection, NDA 202-008, in response to a Complete Response Letter issued by the Division of Medical Imaging Products (DMIP) on March 17, 2011. The proposed indication for Amivid is:

(b) (4)

DMIP consulted the Pediatric and Maternal Health Staff (PMHS) – Pediatrics to evaluate the acceptability of the PREA Waiver Request and review the pediatric use labeling.

BACKGROUND

Amyvid (florbetapir F 18) Injection is a radiopharmaceutical product that binds with avidity and selectivity to β -amyloid plaques derived from human brain tissue obtained post-mortem from patients with AD pathology.²

PREA Waiver Request

The Sponsor submitted a request for a full waiver of pediatric studies with Amyvid, in accordance with the Pediatric Research Equity Act (PREA). The Sponsor requested a full waiver because studies in the pediatric population are impossible or highly impracticable because Alzheimer's disease is an adult-related condition.³

Proposed Pediatric Use Labeling

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

DISCUSSION AND CONCLUSIONS

The Sponsor is seeking a full waiver of pediatric studies under PREA because the proposed use for Amyvid is in PET imaging of β -amyloid neuritic plaques in the brains of adult patients with cognitive impairment being evaluated for suspected Alzheimer's disease (AD). PMHS-

¹ See proposed labeling, October 7, 2011

² See proposed labeling, October 7, 2011

³ See PREA waiver request, December 2, 2011

Pediatrics agrees with the Sponsor that a full waiver of pediatric studies under PREA is appropriate for the proposed indication, as Alzheimer’s disease does not occur in the pediatric population, except in rare diseases (e.g., Progeria). PMHS - Pediatrics did not find any evidence of potential clinically important off-label pediatric use of florbetapir F 18 in published literature. However, if DMIP is aware of potential pediatric use for Amyvid, then a Written Request for pediatric studies under the Best Pharmaceuticals for Children Act (BPCA) should be considered.

The Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted. 21 CFR 201.57(c)(9)(iv) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. The Sponsor proposed pediatric use language for Amyvid that does not meet the requirements set forth in 21 CFR 201.57(c)(9)(iv).

RECOMMENDATIONS

Pediatric Use Labeling

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

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/s/

JEANINE A BEST
12/07/2011

HARI C SACHS
12/07/2011

I concur and am also signing on behalf of CAPT Lisa L. Mathis, Associate Director, OND- PMHS

LISA L MATHIS
12/20/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

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

Application: NDA 202-008

Name of Drug: AMYVID (Florbetapir F 18 Injection)

Applicant: Avid Radiopharmaceuticals

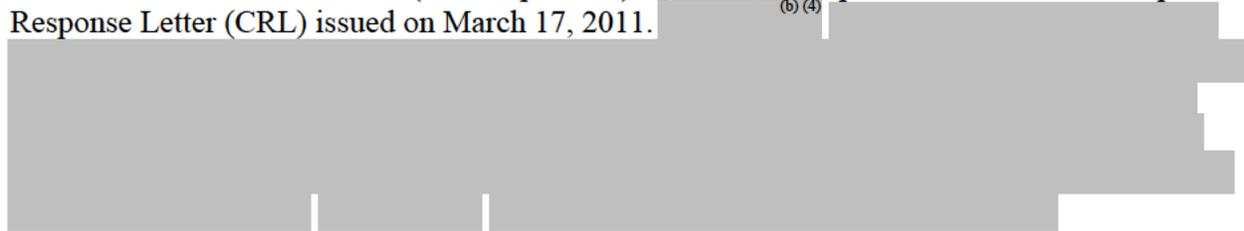
Labeling Reviewed

Submission Date: October 7, 2011

Receipt Date: October 7, 2011

Background and Summary Description

Avid resubmitted AMYVID™ (florbetapir F 18) Injection, in response to the FDA's Complete Response Letter (CRL) issued on March 17, 2011. (b) (4)



FDA provided labeling comments in the March 17, 2011 CRL letter. Avid revised the proposed Prescribing Information (PI) in response to the CRL letter.

This NDA is an electronic submission which follows the eCTD guidance. Draft labeling was submitted for the PI and Carton and Container. The PI was submitted in PLR format. Electronic Content of Labeling was submitted in SPL format.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

Recommendations

All labeling issues identified on the following pages with an “X” will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues. The resubmitted labeling will be used for further labeling discussions.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

General comments

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPERCASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

Highlights Limitation Statement

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Product Title

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

Initial U.S. Approval

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

Boxed Warning

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this

- Highlights Limitation Statement** (required statement)
- Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
- Initial U.S. Approval** (required information)
- Boxed Warning** (if applicable)
- Recent Major Changes** (for a supplement)
- Indications and Usage** (required information)
- Dosage and Administration** (required information)
- Dosage Forms and Strengths** (required information)
- Contraindications** (required heading – if no contraindications are known, it must state “None”)
- Warnings and Precautions** (required information)
- Adverse Reactions** (required AR contact reporting statement)
- Drug Interactions** (optional heading)
- Use in Specific Populations** (optional heading)
- Patient Counseling Information Statement** (required statement)
- Revision Date** (required information)

statement is not necessary.

Recent Major Changes (RMC)

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

Indications and Usage

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

Contraindications

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference contraindications section (4) in the FPI.

Adverse Reactions

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

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

Patient Counseling Information Statement

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

Revision Date

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and crossreference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

Adverse Reactions

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- X** For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:
“The following adverse reactions have been identified during post approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Use in Specific Populations

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

Patient Counseling Information

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence.

For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Sharon Thomas

10-19-11

Regulatory Project Manager

Date

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/s/

SHARON P THOMAS
10/19/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 19, 2011

TO: Sharon Thomas, Regulatory Project Manager
Qi Feng, MD, Medical Officer
Division of Medical Imaging Products

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

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202008

APPLICANT: Avid Radiopharmaceuticals, Inc.

DRUG: florbetapir F 18 injection (Amyvid)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: PET molecular imaging agent for imaging of beta-amyloid aggregates
in the brain

CONSULTATION REQUEST DATE: October 4, 2010

DIVISION ACTION GOAL DATE: March 14, 2011

PDUFA DATE: March 17, 2011

I. BACKGROUND:

Reproducible and valid methodologies for detection of cerebral beta-amyloid plaque accumulation in disease-specific pathologies related to cognition, such as Alzheimer's dementia, are important in health service delivery for the aging population. The 18F-labeled agent florbetapir F18 is one of these positron emission tomography (PET) imaging compounds tested, with well-tolerated and acceptable radiation dosimetry at 370 Megabecquerel (MBq) (10 milliCurie [mCi]).

The sponsor submitted an adequate and well-controlled study as summarized below in support of the use of florbetapir injection in Positron Emission Tomography molecular imaging agent for cerebral imaging of beta-amyloid aggregates.

STUDY PROTOCOL 18F-AV-45-A07

The primary research question was whether or not florbetapir-PET accurately detected the presence and density of beta-amyloid aggregates. This diagnostic test evaluation study was designed to test the (1) relationship between brain amyloid measures using florbetapir F18 PET imaging and true levels of amyloid burden as measured by histopathological assessment at autopsy, and (2) specificity of florbetapir-PET to identify accurately the absence of amyloid pathology.

For the "autopsy cohort," 152 subjects were enrolled from various institutions (e.g., hospice/hospital/nursing home) and late-life (longitudinal studies of aging) groups to yield 35 autopsies within a year following the PET imaging procedure. Specifically, study subjects 18 years of age or older, at various cognitive status levels (normal cognition to dementia), who had a projected life expectancy of 6 months or less (or other end-of-life subjects who were already enrolled in longitudinal studies of aging) and who could tolerate a 10-minute PET scan were eligible to enroll in the autopsy cohort. The endpoint was evaluated by three independent imaging physicians who evaluated the florbetapir-PET scans in a randomized blinded fashion. The neuropathology analyses were independently performed and examiners were also blinded to any clinical information, image data, or reading results.

For the "specificity cohort," young (i.e., age 18 to 40 years) healthy individuals were enrolled for specificity analysis of florbetapir-PET imaging scans. Control scans were randomly mixed with scans rated positive (i.e., median rating of 2, 3 or 4) from the autopsy cohort for the blinded reading by three additional independent imaging physicians for the specificity evaluation. Specifically, healthy male and female subjects, who had no known risk factors for Alzheimer's disease (AD), and who could tolerate a 10-minute PET scan were eligible to enroll.

The primary efficacy was assessed via primary correlation and specificity analyses for this diagnostic test evaluation study. The study was conducted at 34 study centers in the United States, 25 of which enrolled at least 1 subject, with a total of 226 subjects enrolled in the study.

Two clinical sites and the applicant were selected for inspection. These clinical sites enrolled a large number of study subjects, which could potentially affect efficacy results for this new molecular entity's use as a PET molecular imaging agent. Further, DMIP sought clarification regarding Site 145's physician not being present at "pre- and post-dose" with the nuclear imaging drug administration. The applicant was inspected to evaluate adherence to regulatory requirements as the product is a new molecular entity.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site	Insp. Date	EIR Received Date	Final Classification
Adam Fleisher, MD	Phoenix, AZ	18F-AV-45-A07 Site #145 (n=20)	12/6-12/13, 2010	Pending	Pending (Preliminary: NAI)
Ralph Edward Coleman, MD	Durham, NC	18F-AV-45-A07 Site #217 (n=25)	11/15-11/22, 2010	NAI	NAI
Avid Pharmaceuticals, Inc.	Philadelphia, PA	SPONSOR	1/3-1/7, 2011	Pending	Pending (Preliminary: NAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Adam Fleisher, MD/Site 145

Banner Alzheimer's Institute
901 East Willetta Street
Phoenix, AZ 85006

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from December 6-13, 2010.

A total of 20 subjects were screened, enrolled and completed the study. There was no under-reporting of deaths or SAEs. An audit of all screened study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

Unblinded PET scan results were forwarded to the study pathologist. Blinding procedures were also observed, such as study blinding related to subject demographic information, medical history, and screening information.

The physician was present at screening, prior to enrollment, post-dose administration and prior to discharge post-imaging as required by the protocol. Hospital staff (including nurses, physician assistants and radiologists) was present also at pre-dose and during the conduct of the imaging studies.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data in support of efficacy and safety from this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Ralph Edward Coleman, MD /Site #217

Duke University
PET facility, Room 0402
Yellow Zone, Duke South
Campus Box 3949
Durham, NC 27710

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 15-22, 2010.

A total of 31 subjects were screened, 26 subjects were enrolled, and completed the study. There was no under-reporting of adverse events noted. An audit of 100% of enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Inspection revealed that the study was conducted adequately. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

SPONSOR INSPECTION

3. Avid Radiopharmaceuticals, Inc.

3711 Market Street, 7th Floor
Philadelphia, PA 19104

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from January 3-7, 2011.

The inspection evaluated principally documents related to study monitoring visits and correspondence. The following documents for Sites #145 and #217 were inspected: Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, communication with the Sponsor and drug accountability, staff training and site monitors. Additionally, 45 study subject records related to Case Report Forms and blinded reads were reviewed during the inspection.

b. Limitations of inspection

None.

c. General observations/commentary

Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites and monitoring of the investigator sites was considered adequate.

For the study subject records reviewed at the sponsor's site, there was no evidence of under-reporting of adverse events and that the primary efficacy endpoints data were verifiable.

No discrepancies were noted. Sponsor appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data in support of efficacy and safety from this Sponsor oversight appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections two U.S. clinical investigator sites and Sponsor were inspected in support of this application, for Protocol 18F-AV-A07. The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

Note: Observations noted above, for Dr. Fleisher's site and Sponsor are based on the preliminary communications from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

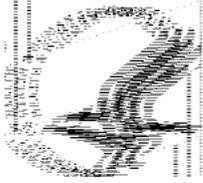
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ANTHONY J ORENCIA
01/19/2011

TEJASHRI S PUROHIT-SHETH
01/19/2011



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: January 11, 2011 **Date Consulted:** October 4, 2010

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Drug: Amyvid (florbetapir F 18), NDA 202-008

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of the Amyvid labeling.

Consult Question: Please review the proposed label for NDA 202-008 as it relates to pregnancy and lactation.

INTRODUCTION

Avid Radiopharmaceuticals, Inc. (Avid) submitted a New Drug Application, NDA 202-008 for Amyvid (florbetapir F 18) Injection on September 17, 2010. Amyvid is a diagnostic radiopharmaceutical with a proposed indication for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β -amyloid, a defining pathology of Alzheimer's disease (AD), which is the most common type of dementia (50-70%). Avid requested and was granted a priority review citing the following reasons:

1. Alzheimer's disease is a fatal disease.
2. Long-standing criteria established by the expert scientific community has identified the presence of β -amyloid pathology at autopsy as a primary component of the post-mortem diagnosis of Alzheimer's disease. Today, there is emerging consensus that biomarkers of β -amyloid pathology may enhance the validity of the clinical diagnosis of AD during life, especially at its earliest symptomatic stage.
3. The ante-mortem diagnosis of Alzheimer's disease has been hindered by the absence of a validated non-invasive biomarker of β -amyloid pathology in the brain.
4. Florbetapir-PET imaging of β -amyloid aggregates in the brain addresses this unmet need for a biomarker of β -amyloid pathology in the diagnosis and management of a potentially serious pathological condition.
 - a. In patients with signs or symptoms of cognitive impairment, the absence of β -amyloid aggregates in the brain by florbetapir-PET indicates that Alzheimer's disease may be ruled out with a high degree of specificity. This would direct the physician to pursue an alternative diagnosis and management pathway for such patients.
 - b. The presence of β -amyloid aggregates as determined by florbetapir-PET imaging is supportive of a clinical diagnosis of AD, providing the physician with a complementary tool for the correct diagnosis of Alzheimer's disease in patients with cognitive impairment.
5. Identification and quantification of β -amyloid aggregates in the brain with florbetapir-PET may facilitate the evaluation and development of new β -amyloid-modulating therapies.
6. There are no marketed products which provide similar information regarding the presence or absence of β -amyloid pathology in the human brain during life.

Based on the FDA Guidance "Medical Imaging of Drug and Biologic Products Part I: Conducting Safety Assessments", Avid requested and FDA granted a waiver of reproductive toxicology studies, as the intended population for florbetapir F 18 is patients with Alzheimer's

disease, who are primarily elderly males and post-menopausal females. Additionally, Avid provided the follow as a rationale for the waiver:

1. The intended Results of single and repeat-dose toxicity studies with non-radioactive AV-45 (¹⁹F-AV-45) have not identified any drug-related toxicity in animals.
2. Pharmacokinetics and distribution properties of florbetapir F 18 suggest low risk to patients.
3. A single-dose distribution study (¹⁸F-AV45-A02) of florbetapir F 18 in 9 healthy volunteers using a validated assay showed that the reproductive organs received low exposure of radiation.

The Division of Medical Imaging Products (DMIP) consulted the Maternal Health Team on October 4, 2010, to review the Amyvid proposed label as it relates to pregnancy and lactation.

BACKGROUND

Alzheimer's Disease

Alzheimer's disease (AD) is an irreversible, progressive brain disease that slowly destroys memory and cognitive functioning, eventually leading to the inability to carry out simple tasks, including activities of daily living. It is the most common form of dementia in older people, with symptoms first appearing after age 60. It is estimated that approximately 5.1 million Americans may have Alzheimer's disease, for which there is no cure. The disease is categorized as mild to severe AD, with symptoms ranging from mild memory problems progressing to inability to communicate, with complete dependency on others for care and eventual shut down of body functions¹. Changes in the Alzheimer's brain occur over a long period of time and damage to brain cells or neurons appear in two forms:

- Beta-amyloid (β-amyloid) Plaques: clumps of protein that may interfere with communication between brain cells.
- Tau Protein Tangles: Tau is a protein that normally occurs in threads in the brain to support normal brain function. In the Alzheimer's brain, tau protein threads undergo alteration that causes them to become tangled. These tangles are thought to cause serious damage to neurons².

Diagnosis of AD usually occurs by ruling out other causes of symptoms via a series of laboratory tests, neuropsychological testing and brain imaging. Positron emission tomography (PET) is one type of imaging used to detect less active areas of the brain and density of amyloid plaques. Although there are diagnostic tests and imaging to rule out other causes and symptoms similar to those in Alzheimer's patients, there is currently no diagnostic test to positively identify changes

¹ Website: <http://www.nia.nih.gov/Alzheimers/Publications/adfact.htm>, National Institute on Aging, National Institutes of Health

² Website: <http://mayoclinic.com/health/alzheimers-disease/DS00161>, Mayo Foundation for Medical Education and Research (MFMER), January 17, 2009

associated with Alzheimer's disease. Currently, Alzheimer's disease can only be confirmed by post-mortem examination of the brain³.

Radiopharmaceutical Use in Pregnancy and Lactation

Diagnostic procedures utilizing radiopharmaceuticals may become medically necessary for women during pregnancy or lactation. Exposure of an embryo, fetus or nursing child to radiopharmaceuticals may result from placental transfer, exposure to maternal tissues (breast or bladder) or via breast milk after maternal radionuclide administration⁴. The potential for fetal harm depends on the fetal gestational age and the dose of radiation received⁵. For lactating women, interrupting breast feeding for a period of time may be necessary with some diagnostic radiopharmaceuticals⁶. When diagnostic procedures with radiopharmaceuticals become medically necessary for a pregnant or lactating women, efforts should be exercised to reasonably minimize exposure of the women and subsequent fetal or infant exposure⁷.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations, but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides the Maternal Health Team's recommended revisions to the highlights, pregnancy and nursing mothers sections of the sponsor's proposed labeling. Appendix A of this review provides a tracked-changes version of labeling that highlights the recommended MHT revisions.

³ Website: <http://mayoclinic.com/health/alzheimers-disease/DS00161>, Mayo Foundation for Medical Education and Research (MFMER), January 17, 2009

⁴ Website: http://rpop.iaea.org/RPOP/RPoP/Content/SpecialGroups/1_PregnantWomen/index.htm, International Atomic Energy Agency, 2010.

⁵ Website: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/Pregnancy.aspx. American College of Radiology, 2008.

⁶ Website: <http://hps.org/physicians/>, Health Physics Society, December 2009.

⁷ Website: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/Pregnancy.aspx. American College of Radiology, 2008.

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

/s/

TAMMIE B BRENT HOWARD
01/18/2011

LISA L MATHIS
01/18/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 202-008 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: proposed: Amyvid Established/Proper Name: Florbetapir F 18 Injection Dosage Form: Sterile Injectable Strengths: 370MBQ/10 mL F18 in <=10 mL sterile solution		
Applicant: Avid Radiopharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: September 17, 2010 Date of Receipt: September 17, 2010 Date clock started after UN:		
PDUFA Goal Date: March 17, 2011		Action Goal Date (if different):
Filing Date: November 16, 2010		Date of Filing Meeting: October 14, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Florbetapir F 18 is indicated for PET Imaging of beta-amyloid aggregates in the brain.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov/9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 79, 511				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				N/A
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				N/A
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

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

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

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

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

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

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

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

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

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): February 13, 2009 <i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 19, 2010 <i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 14, 2010

BLA/NDA/Supp #: NDA 202-008

PROPRIETARY NAME: proposed: Amyvid

ESTABLISHED/PROPER NAME: Florbetapir F 18 Injection

DOSAGE FORM/STRENGTH: 370 MBq florbetapir F 18 in <=10 mL sterile solution for intravenous injection.

APPLICANT: Avid Radiopharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Positron Emission Tomography (PET) imaging of beta-amyloid aggregates in the brain.

BACKGROUND: NDA 202008 is submitted by Avid Radiopharmaceuticals, with a proprietary name of Amyvid, and an established name of florbetapir F 18 injection.

This New Molecular Entity (NME) is a diagnostic radiopharmaceutical, indicated for PET imaging of beta-amyloid aggregates in the brain. A negative florbetapir PET scan is clinically useful in ruling out the presence of beta-amyloid, a defining pathology of Alzheimer’s disease (AD).

The objectives of the NDA is to test the relationship between measurements of amyloid burden using Amyvid PET imaging and levels of amyloid burden determined at autopsy and to test the specificity of Amyvid-PET to accurately identify the absence of amyloid pathology.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Thomas	Y
	CPMS/TL:	Kyong “Kaye” Kang	N
Cross-Discipline Team Leader (CDTL)	Alex Gorovets		Y
Clinical	Reviewer:	Qi Feng	Y
		Lucie Yang	Y

	TL:	Alex Gorovets	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Young Choi	Y
Biostatistics	Reviewer:	Lan Huang	Y
	TL:	Jyoti Zalkikar	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sunny Awe	Y
	TL:	Adebayo A Lanionu	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ravindra Kasliwal	Y
	TL:	Eldon Leutzinger	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	N
	TL:	Todd Baugh	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Anthony Orenca	Y
	TL:	Tejashri Purohit-Sheth	N

Other reviewers	Charles Ganley, Office Director	
Other attendees	Ross Felice, Clinical Reviewer	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: There will be an AC meeting scheduled on 01/20/2011 for independent advice and recommendations to the FDA on scientific and technical matters related to this NDA.</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

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Appears This Way On Original

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

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

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Rafel Dwaine Rieves, Division Director	
21 st Century Review Milestones (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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
10/22/2010