

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202008Orig1s000

OTHER ACTION LETTERS



NDA 202-008

COMPLETE RESPONSE

Avid Radiopharmaceuticals, Inc.
Attention: Alan P. Carpenter, Ph.D.
3711 Market Street, 7th Floor
Philadelphia, PA 19104

Dear Dr. Carpenter:

Please refer to your New Drug Application (NDA) dated September 17, 2010, received September 17, 2010, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Amyvid™ (florbetapir F 18) Injection.

We acknowledge receipt of your amendments dated:

September 28, 2010	November 30, 2010	January 31, 2011 (2)
October 10, 2010	December 3, 2010	February 4, 2011
October 25, 2010	December 7, 2010	February 16, 2011(2)
November 9, 2010	December 22, 2010	February 17, 2011
November 17, 2010	January 7, 2011	February 18, 2011

The originally proposed indication was altered during the review cycle, as discussed at the January 20, 2011 meeting of the Peripheral and Central Nervous System Advisory Committee. The following is your most recent revised indication proposal:

(b)
(4)

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. During the terminal portion of the review cycle (February, 2011), you submitted revised labeling and two new study reports that described “reread” results for Study A07 and a selected portion of Study A05. Our examination of this information found that it did not

sufficiently address our findings from a detailed review of the clinical data supplied within the original submission.

2. As discussed at the January 20, 2011 advisory committee, insufficient information has been submitted to support the approval of your application. The majority of committee members voted against approval at the present time and the discussion focused upon the need for the development of clinically-applicable reader training materials and verification of the reproducibility and reliability of image interpretations as performed in the clinically-applicable manner.
3. Supply the reader training program materials you propose for marketing implementation. Portions of your submission referred to a potential website, to professional society training as well as other electronic media. Develop your training program materials in a manner that definitively establishes the elements of the program. This program should provide sufficient methods to help ensure reliable interpretation of Amyvid images and optimize image reporting. Submit the materials in a manner sufficient for our detailed review. We anticipate the need to incorporate these materials into labeling or another format that will preclude ad hoc modifications of the materials in the post-marketing setting. In addition to any other items, address the following topics within the program:
 - a. Provide background on Amyvid, including a description of [REDACTED] (b) (4) and how Amyvid can be used [REDACTED] (b) (4). Define [REDACTED] (b) (4).
 - b. Describe the strengths and limitations of Amyvid imaging, including its inability to diagnose any disease or condition, including Alzheimer's disease.
 - c. Describe the procedures for interpreting Amyvid images, including any unique hallmarks or signals for distinction of a "positive" versus a "negative" image.
 - d. Include a procedure for representative image display and a test image assessment.
 - e. Describe the clinical meaningfulness of Amyvid image findings.
 - f. Describe the procedure for reporting the image findings. We recommend the use of a template text that briefly summarizes the findings as well as the strengths and limitations of these findings.

Additionally, it would be helpful to explain how the training program for marketing implementation evolved from the training that was utilized in the initial reads of study A05 and A07 and any subsequent reads utilizing a binary read methodology (studies A08 and A09).

4. Using the established reader training program materials, supply information from a study that reinterprets the images obtained in Studies A07 and A05. This study is necessary to

establish the validity of the training program for marketing implementation. Study A08 and Study A09 are not sufficient because they do not employ the exact training materials and methods that will be used in clinical practice. Develop a protocol and conduct the study in a manner representative of image interpretation in the proposed clinical setting. Reader training methods for these studies should not extend beyond the materials included within the established reader training program.

- a. Images of subjects in the autopsy cohort of Study A07 (at least 152 subjects, see 4.f. below) and all subjects in Study A05 (n=184) are expected to be randomized together in the reading queue for reinterpretation by each reader.
- b. In the development of the analytical plans for Study A07 images from subjects with histopathology, in addition to any other analyses, include an exploratory analysis of performance characteristics (sensitivity, specificity, correlates) in comparison to aspects of the autopsy truth standard relevant to your proposed clinical indication, e.g., the modified CERAD neuritic plaque density.
- c. Plan for analyses that assess the reproducibility of image interpretations among the readers. Before initiating these studies, it is important that you discuss with us the number of readers to include in these studies and the success criteria.
- d. We strongly encourage you to submit the protocols for these studies for our review, prior to your initiation of the studies. Supply the protocols to your Investigational New Drug (IND) 79-511 application.
- e. The previous training programs for readers included hands on training and readings conducted at central facilities. For these studies, it is preferable that the readings not be conducted at a central lab or facility. We are interested in having the readings conducted in a manner and in conditions similar to what will occur with the marketing of the drug.
- f. The primary efficacy population for Study A07 is rather small, with only 29 subjects. Any additional data from patients originally enrolled in the autopsy cohort who have died since the submission of this application, should have brain histopathology analyzed and readings of their scans included.

5. During the review cycle, you modified your drug's proposed indication to state that it is indicated for (b) (4)

The modified indication statement also notes, (b) (4)

- a. Your NDA contained multiple amendments that were intended to support your drug's modified indication. However, the NDA did not contain a single cohesive,

detailed description of the basis for the modified indication. For example, the amendment from December 2, 2010 appeared to rely upon a publication (Neurology 2005; 64:834; authored by Bennett) as the main support for your modified indication. Multiple other publications referenced throughout your application appeared pertinent to the modified indication. The multiple data sources were not organized and presented in a manner that allowed us to verify the appropriateness of your modified indication.

- b. Supply a document that contains a detailed justification for your use of the phrase,

(b) (4)

- c. Develop the justification document to include appendices of relevant publications and data sources. This information may importantly impact your labeling. As currently proposed, your labeling does not sufficiently define the phrase,

(b) (4) and does not appear to contain sufficient justification for your proposal (b) (4)

To illustrate one aspect of our concern, you refer to (b) (4) in a manner that appears to represent your interpretation of neuritic plaque densities assessed by histopathologic staining of brain tissue. If this is your interpretation, we anticipate that labeling would describe the neuritic plaque density observation, not use an inference to (b) (4)

- d. It is important that labeling include a discussion of the limitations of Amyvid PET with regard to the diagnosis of Alzheimer's disease. Your revised labeling includes (b) (4)

(b) (4). In Study A05, some healthy subjects and patients with mild cognitive impairment had images read as "positive" for amyloid. For those with mild cognitive impairment and a "positive" amyloid scan, it could be inferred that (b) (4)

You have not provided sufficient evidence to show that Amyvid may (b) (4)

Please provide a detailed justification for use of the phrase (b) (4)

- e. In addition to other items within your justification document:

- i. Define the various types of amyloid plaques and the extent to which they are imaged with Amyvid;
- ii. Comment specifically upon Amyvid imaging of diffuse amyloid plaques and the extent to which any detection has (b) (4);

- iii. Develop your (b) (4) discussion in a method conducive to potential incorporation of the major points into your drug's prescribing information.
 - f. Within the justification document clearly define the association among the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scoring of neuritic plaque density, any modification of this scoring and important contemporary criteria for the neuropathologic diagnosis of Alzheimer's disease. Present this material in a manner that cites the strengths as well as the limitations of the available data. Anticipate the potential need to incorporate the major points of this discussion within your drug's prescribing information.
6. In study A08, patient 057-007 had a CERAD score of "none" but 8 of 9 readers designated this as a positive scan for amyloid. Please explain how this occurred.

PRODUCT QUALITY

7. Revise the bulk product vial label to include the following:
- Relocate established name (Florbetapir F18 Injection) below the trademark AMYVID™.
 - Make space for NDC number above trademark AMYVID™ and place it in the upper left corner of the label.
 - Place word "Sterile" in the upper right corner of the label.
 - Place strength statement below the established name (Florbetapir F18 Injection) on the label.
 - Place statement "for intravenous use" below the strength statement.
 - Place "Rx Only" prominently on the label.
 - Place quantitative composition statement on the label.
 - Place storage statement on the label.
8. Revise the carton (lead shield) label to include the following:
- Relocate established name (Florbetapir F18 Injection) below the trademark AMYVID™.
 - Make space for NDC number above trademark AMYVID™ and place it in the upper left corner of the label.
 - Place word "Sterile" in the upper right corner of the label.
 - Place strength statement below the established name (Florbetapir F18 Injection) on the label.
 - Place statement "for intravenous use" below the strength statement.
 - Make "Rx Only" more prominent on the label.
 - Change the quantitative statement to express sodium chloride and sodium ascorbate content in mg/ml units (e.g., Each mL contains, xx – yy mg florbetapir,

XX mCi florbetapir F 18 at calibration, XX mg sodium chloride, xx mg sodium ascorbate, and 0.1mL (10%) ethanol)

- Change the storage statement to “Store at USP controlled room temperature 25°C (77°F)”
- Place Batch Number on the label.

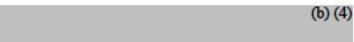
9. Revise the description section of the package insert as follows:



LABELING

10. In the Highlights section of the label, revise the  (b) (4) to the following:



11. Modify the  (b) (4) section, in Highlights as follows:



13. In the package insert, revise section 8.1, Pregnancy to the following:

- Pregnancy Category C: [REDACTED] (b) (4)
[REDACTED] Amyvid should be administered to a pregnant woman only if clearly needed.

13. Modify section 8.3, Nursing Mothers to the following:

- [REDACTED] (b) (4)

14. Revise section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility to the following:

- In an *in vitro* bacterial reverse mutation assay (Ames test), increases in the number of revertant colonies were observed in 2 of the 5 strains exposed to [REDACTED] (b) (4) (19F-AV- 45, the non-radioactive form of florbetapir F 18). In a chromosomal aberration *in vitro* study with cultured human peripheral lymphocytes cells, [REDACTED] (b) (4) did not increase the percent of cells with structural aberrations with 3-hour exposure with or without activation; however, 22 hour exposure produced a statistically significant increase in structural aberrations at all tested concentrations. Potential *in vivo* genotoxicity of [REDACTED] (b) (4) was evaluated in a mouse micronucleus study. In this assay, [REDACTED] (b) (4) did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level, 372 µg/kg/day, when given twice daily for 3 consecutive days.

[REDACTED] (b) (4)

15. Submit draft labeling that incorporates the requested revisions cited above. In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

16. Submit draft carton and container labeling revised based upon the requested alterations, as listed above.

FACILITY INSPECTIONS

During a recent inspection of the your manufacturing facility in Philadelphia, PA, PETNET manufacturing facilities in Kent, WA, Palo Alto, CA and North Wales, PA, and Cardinal Health manufacturing facilities in Charlotte, NC and Orlando, FL, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory inspection reports for all facilities must be received before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Charles J. Ganley, M.D.
Director
Office of Drug Evaluation IV (ODE IV)
Center for Drug Evaluation and Research

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

/s/

CHARLES J GANLEY
03/17/2011