

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202008Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	April 5, 2012
From	Charles J. Ganley, M.D.
Subject	Office Director Decisional Memo
NDA #	202008
Applicant Name	Avid Pharmaceuticals, Inc.
Date of Submission	October 7, 2011
PDUFA Goal Date	April 7, 2012
Proprietary Name/Established (USAN) Name	Amyvid Florbetapir F18 Injection
Dosage Form	Amyvid is to be supplied in 10 ML vials (b) (4) ; the recommended dose is 370 MBq (10 mCi) administered intravenously to adults.
Action	Approve

The Division Director memo nicely outlines the history of Amyvid and the data summary to support the approval of the application. Amyvid was discussed before an advisory committee in January of 2011 and Avid sent a complete response letter on October 7, 2011. The primary deficiency involved the ability of readers, without training, to interpret the scan results and the need for an e-based training program that would improve inter-reader interpretation and maintain a high level of sensitivity and specificity. All of the scans read in the initial application were done after extensive face to face training. The sponsor has provided data to support an e-based training program and the application can be approved.

In addition:

- The proprietary name, Amyvid, was found acceptable.
- The Pediatric and Maternal Health staff has provided labeling for pregnancy and nursing. It is unlikely that the population of women likely to become pregnant would need to have this test conducted.
- Public Citizen sent a letter to the FDA on February 21, 2011 requesting that the FDA not approve Amyvid. Many of the issues cited in the letter were raised by FDA during the first cycle review. All of these issues have been addressed. A response was sent to Public Citizen on March 2, 2012.
- A full pediatric waiver was granted for this product.
- Exclusivity of 5 years is recommended.
- Facility inspections are complete with no outstanding issues.
- In vitro and ex vivo studies demonstrate that Florbetapir binds to aggregated amyloid in the human brain. There are no outstanding pharm tox issues.
- There are no chemistry or microbiology issues. All inspections have been completed and there are no outstanding issues.
- A DSI investigation of study PT01 found that the study was conducted in accordance with the protocol and contractual agreement with the contract research organization.
- The sponsor has agreed to post marketing commitments for two studies. One trial will evaluate the quality of the scan reads in the real world and the other will assess possible quantitative measures (SUVr) to improve reading sensitivity and specificity. The clinical pharmacology reviewer recommended that the study evaluating SUVr be a post-marketing requirement. The CDTL did not agree with it being a PMR to evaluate SUVr because she did not believe that it fulfills the requirements of a PMR (i.e. it is not addressing a serious safety concern). She did recommend that a post-marketing commitment is reasonable to collect information. I agree with this recommendation.

Study PT01

This study was conducted using 5 readers to determine whether training material provided on a compact disc to readers will provide adequate training to readers of the scans. The study addressed the major deficiency of the complete response letter.

- The sensitivity and specificity of the 5 readers ranged from 69% – 92% for sensitivity and 90% – 95% for specificity when the autopsy cohort was evaluated (N = 59).
- There were thirteen subjects who died greater than 12 months after the scan was performed. If just the cohort who had the scan conducted within 12 months of death are included in the analysis, the sensitivity ranged from 75% - 100% and the specificity ranged from 89% - 100% (N = 46).
- Table 8 in the CDTL review lists the six subjects who pathologic diagnosis (autopsy cohort) did not match the scan read.
 - Two of the autopsy cohort were read as negative by all of the readers but were found to be positive for beta amyloid on histopathology. They had their scans performed 14 and 22 months prior to death. If this is to be believed then the amount of B amyloid at one point in time (particularly if the scan is determined to be negative), may not be predictive of future deposition of amyloid.
 - For the remaining four patients, in one case head motion during the scanning may have impacted on the quality of the scan and in three cases there is no adequate explanation provided by the sponsor. It should be noted that in two of the three, a central read made the correct diagnosis, so it may be that self training may have certain limitations.
- Inter-reader reproducibility analyses showed overall Fleiss kappa statistic of 0.83 (95% C.I.: 0.78 to 0.88) with a lower bound of 0.78 which exceeded the pre-specified success criterion of 0.58.
- There were 33 images that were read twice by each reader. The intra-reader agreement was 96% and median kappa was 0.94.

Conclusion

The compact disc based training allowed readers to interpret the scans with good sensitivity and specificity.

Should the training be required and be mandatory?

There were a variety of opinions expressed including that no training by the sponsor should be required. After much internal discussion, it was decided that the training should not be mandatory but should be recommended in the labeling. There was concern that making it mandatory, such as face to face training or even through various e-methods (web-based, compact disc), would be cumbersome to require and track. This was also unprecedented, in that, other imaging applications, where in some cases the scans are difficult to read, we have not required a sponsor to develop a training program. The sponsor developed a training program and validated its ability to train readers (although we acknowledge there is no baseline with which to compare) resulting in an acceptable sensitivity and specificity. We have described the content of the training program in the labeling rather than treat the content as a separate entity. The following language is included in the labeling: *Amyvid images should be interpreted only by readers who successfully complete a special training program. Training is provided by the manufacturer using either an in-person tutorial or an electronic process.*

What are the limitations of the scan?

There are several limitations of the scans.

- Brain B amyloid can be found in people who do not have a diagnosis of Alzheimer's disease. The results of the scan have to be considered with other information available about the patient.
- The interpretation of the scan may be dependent on the population tested.
 - For a patient with mild cognitive impairment (MCI) who is scanned, a negative scan simply means that B amyloid was not detected at that point in time. This may be reassuring to someone who is concerned that their cognitive impairment is the beginning of Alzheimer's disease. There are limitations with this, however, because it only reflects that point in time and could change in subsequent years. Likewise, a positive scan in an MCI patient does not mean they have Alzheimer's disease. There are no longitudinal studies in MCI patients that help explain what the test result means related to future development of dementia. Ideally, it would be beneficial to have longitudinal study data that describes the percent of subjects with positive or negative scans who go on to develop dementia over a specific time period in an MCI population.
 - In a patient with dementia, a negative scan may encourage the clinician to entertain diagnoses other than Alzheimer's disease.
- The scans are difficult to interpret and it is important that readers be trained. The sponsor has committed to conducting a post-marketing study to evaluate the quality of the reads conducted by readers in the community.

Conclusion

Approval of the application is recommended by the review team and I agree with their recommendation. We recognize that there are limitations with any diagnostic tests. This test will provide the clinician with additional information that can be factored into the evaluation of patients with cognitive decline.

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Director, ODEIV

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/s/

CHARLES J GANLEY
04/05/2012