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October 21, 2011

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: New Drug Application (NDA), # 202-008, for florbetapir F18 injection (Amyvid)

Dear Dr. Woodcock:

As you are aware, in our letter to you dated February 21, 2011,¹ and in our recently published letter to the editor of the *Journal of the American Medical Association*,² we urged the Food and Drug Administration (FDA) not to approve Avid Pharmaceuticals' New Drug Application (NDA), # 202-008, for florbetapir F18 injection (Amyvid) because of the significant inter-reader variability that was seen in the single phase 3 clinical trial evaluating the performance of florbetapir positron emission tomography (PET) imaging. Given such inter-reader variability, such PET scans would have little clinical utility in the evaluation of patients presenting with cognitive deficits or early dementia and suspected of having Alzheimer's disease (AD).

In an editorial just published on-line in the *European Journal of Nuclear Medicine and Molecular Imaging* (copy enclosed),³ experts in the field of PET neuroimaging have identified even more fundamental problems with the results of studies cited by Avid Pharmaceuticals in its NDA that undermine any support for the following proposed indication for florbetapir-PET scans:

Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for [PET] imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β -amyloid in the brain.⁴

In particular, the just-published analysis presented by Moghbel et al reveals the following very troubling aspects of florbetapir-PET imaging:

- There is a striking discrepancy between the distribution of β -amyloid deposits in the brain allegedly shown by florbetapir-PET scans in patients with AD with that

seen with histopathological and immunohistochemical studies of brain samples, which are the gold standards for identifying β -amyloid deposits.

- Imaging studies conducted with florbetapir, as well as virtually any other purported amyloid tracer, consistently have shown the frontal lobe to have one of — if not the — highest standardized uptake values. In contrast, autopsy studies of brain from AD patients have demonstrated that the highest density of β -amyloid deposits was found in the temporal and occipital lobes, whereas the lowest concentration was seen in the limbic and frontal lobes.
- Likewise, multiple studies of other brain imaging modalities in AD patients revealed that the greatest degree of brain atrophy and abnormal metabolism occurred in the temporal and parietal lobes, whereas the lowest degree occurred in the frontal lobes.
- PET imaging with amyloid agents such as florbetapir shows substantial uptake in white matter of the brain, which is believed to be nearly devoid of β -amyloid plaques. Indeed, PET imaging with various purported amyloid agents consistently have shown higher ratios of white matter β -amyloid to grey matter β -amyloid than immunohistochemical tests. This pattern of white matter uptake of amyloid radiotracers such as florbetapir has been largely described as a product of non-specific binding, but has also been speculated to be an artifact of slower clearance rate due to reduced blood flow in the white matter as compared to grey matter.
- Given the size of β -amyloid plaques and the small percentage of total brain area occupied by β -amyloid plaques even in the most severely affected cortical regions, amyloid agents such as florbetapir almost certainly do not have sufficiently greater uptake in β -amyloid deposits than in the background to allow accurate detection of β -amyloid deposits on PET imaging.

Therefore, in addition to the considerable inter-reader variability and inadequate sensitivity and specificity seen with florbetapir-PET scans for diagnosing AD, the analysis by Moghbel et al indicates that florbetapir is not even useful for imaging of β -amyloid aggregates in the brain, the indication proposed by Avid Pharmaceuticals.

A review of the FDA's briefing materials for the January 20, 2011 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee⁵ suggests that FDA review staff were unaware or did not consider the issues identified by Moghbel et al in their editorial.

We note that Dr. Abass Alavi, the senior author of the enclosed editorial, is a professor of radiology and the former chief of the Division of Nuclear Medicine at the University of Pennsylvania Medical Center and has conducted pioneering research and clinical work in PET imaging since the early 1970s. He is an internationally recognized expert in advanced medical imaging techniques and the clinical application of PET imaging for the detection and evaluation of many disorders, including dementia, cancer, cardiovascular disease, and infection.

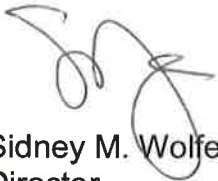
We urge the FDA to withhold taking any further action on NDA # 202-008 for florbetapir F18 injection (Amyvid) until the agency has thoroughly reviewed and considered the analysis presented in the enclosed editorial. The analysis by Moghbel et al further demonstrates that florbetapir-PET imaging is not a useful modality for the evaluation of patients suspected of having AD and should not be approved.

Thank you for considering these comments in this very important matter.

Sincerely,



Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

Enclosure

cc: The Honorable Kathleen Sebelius, Secretary of Health and Human Services
Dr. Margaret A. Hamburg, Commissioner, FDA
Dr. Russell G. Katz, Director, Division of Neurology Products, Office of New Drugs,
Center for Drug Evaluation and Research, FDA

¹ Carome MA, Wolfe SM. Letter to Dr. Janet Woodcock dated February 21, 2011, urging rejection of florbetapir F18 injection (Amyvid). Available at <http://www.citizen.org/hrq1932>. Accessed October 20, 2011.

² Carome MA, Wolfe SM. Florbetapir-PET imaging and postmortem beta-amyloid pathology. JAMA. 2011;305:1857.

³ Moghbel MC, Saboury B, Basu S, et al. Amyloid- β imaging with PET in Alzheimer's disease: Is it feasible with current radiotracers and technologies? Eur J Nucl Med Mol Imaging. Published on-line on October 19, 2011. DOI 10.1007/s00259-011-1960-4.

⁴ Avid Pharmaceuticals, FDA advisory committee briefing document, NDA #202-008, florbetapir F18 injection: advisory committee meeting of January 20, 2011. December 16, 2010. Web page 3. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240266.pdf>. Accessed October 20, 2011.

⁵ Food and Drug Administration. FDA advisory committee briefing document: Peripheral and Central Nervous Systems Drugs Advisory Committee. December 20, 2010. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240265.pdf>. Accessed October 20, 2011.