CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203137Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/OND/ODE-IV

Date: 10/21/2013
From: Shaw T. Chen, M.D., Ph.D., Deputy Director, Office of Drug Evaluation-IV
To: File, NDA-203137
Subject: Approval of NDA 203137, Vizamyl (Flutemetamol F 18), for Positron Emission Tomography (PET) imaging of β amyloid plaque

This is the ODE Director's memo to concur with the approval of this NDA, as recommended by the Division of Medical Imaging Products (DMIP). Flutemetamol F 18 (referred as flutemetamol in this memo) is the second radioactive diagnostic agents proposed for use for PET imaging of the brain for visualization of β amyloid plaque.

Overall, the data submitted in this application support the approval of Flutemetamol F 18 with the indication and other instructions in the proposed labeling. As summarized in the Division Director's memo by Dr. Marzella, reviews by relevant disciplines and facility/data inspections have all been completed. There are no outstanding issues identified in the reviews or inspections that may preclude the approvability of this application. The applicant and FDA have also agreed on the final version of the labeling. No post-marketing studies are considered necessary.

Major regulatory and scientific issues of this NDA are summarized as follows.

EFFICACY – PERFORMANCE OF THE IMAGING AGENT

The conclusion that the performance of flutemetamol is acceptable as an effective PET agent, as reached by the review team and the Division Director, is correct in my view. As summarized in Dr. Marzella' memo and the primary/secondary clinical/statistical reviews, data from Studies 007, 021 and, to a lesser degree, 015, provide the major support for efficacy. Details of these studies and limitation of the clinical data are referred to the aforementioned reviews. For all 3 studies, the performance of the test imaging agent is considered acceptable if the lower bounds of 95% confidence interval for sensitivity and specificity are >70% for at least 3 of the 5 readers. Definitions for the standard of truth and related issues are discussed below for individual studies.

Sensitivity

The results of **Study 007** provide the major support of performance for flutemetamol. Using the whole-brain histopathology as the standard of truth, it successfully met the pre-specified primary endpoint of sensitivity (lower bound of 95% CI $\geq$70% in $\geq$3 readers, see definition above):

Study 007 (n=68)	Reader	Sensitivity (%)	(95% CI)
	1	81	(67, 92)
	2	88	(74, 96)
	3	93	(81, 99)
	4	93	(81, 99)
	5	88	(75, 96)

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This finding is consistent with that of the second supporting study, **Study 021**, which also evaluated the effectiveness of an electronic training program with a new panel of image readers, using data from subjects who participated in earlier studies[1]. The lower bounds of 95%CI were above 70% for all readers, meeting the primary endpoint of sensitivity:

Study 021 (the subset of 135 subjects with a sponsor-defined truth standard)

Reader	Sensitivity (%)	(95% CI)
6	94	(84,99)
7	92	(81,98)
8	90	(79,97)
9	94	(84,99)
10	84	(71,93)

Not surprisingly, the sensitivity results were not affected by the exclusion of 31 young healthy volunteers from this group for lack of histopathology data as the standard of truth (who were presumed negative for amyloid plaque, see CDTL review).

Results of these two studies demonstrated that the sensitivity of flutemetamol as an imaging agent for amyloid is acceptable.

Specificity

For imaging tests that require histopathology data as the standard of truth, reaching the specificity endpoint is often a difficult objective, especially for imaging of the CNS system. For patients with negative histopathology, they are in general not as ill and have less need for brain biopsy or ethically impossible for such invasive procedure (e.g., normal healthy volunteers). Recruitment of terminally ill patients with unrelated diseases (thus negative imaging) for the sole purpose of brain biopsy or autopsy is also rarely easy.

The specificity data for **Study 007** thus suffered from the problem of inadequate number of patients with true negative pathology and imaging. The point estimates were acceptable (in 4 of 5 readers), but the confidence intervals were wide. Two readers (Readers 2 & 5) had a lower bound of 95% CI exceeding 70%, with the third reader (Reader 1) almost met the goal (69%):

Study 007 (n=68)	Reader	Specificity (%)	(95% CI)
	1	88	(69, 98)
	2	92	(74, 99)
	3	44	(24, 65)
	4	80	(59, 93)
	5	92	(74, 99)

The primary analysis of **Study 021**[1] showed higher specificity with inclusion of 31 normal subjects who were presumed to be true negative for amyloid plaques, with lower bounds of 95%CI above 70% in 3 readers (67-68% in the other two readers). The study is thus a success in specificity testing.

[1] A significant subset of 68 patients were from Study 007, thus this study (021) is an expansion of the old study, not a completely independent verification. It is mainly a test of the training program with a different panel of readers.

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Study 021 (the subset of 135 subjects with a sponsor-defined truth standard)

Reader	Specificity (%)	(95% CI)
6	79	(68,87)
7	81	(71,89)
8	93	(85,97)
9	96	(90,99)
10	77	(67,86)

As expected, the specificity dropped when the normal subjects were excluded, with only 2 of the 5 readers had lower bound of 95%CI greater than 70% (with 66% for the third reader):

Study 021 (the subset of 104 subjects with a histopathological truth standard)

Reader	Specificity (%)	(95% CI)
6	68	(54,80)
7	79	(66,89)
8	89	(77,96)
9	72	(58,83)
10	94	(84,99)

If the primary specificity results of Study 021 (including 31 without histopathological truth standard in the cohort of 135 subjects, see above) are to be accepted, then **Study 015** should not be totally dismissed for lack of histopathological truth standard. It provides some additional support for specificity, though not as robust as the other two studies with histopathological truth standard (see also medical review for Dr. Davis' concern about investigators' bias):

Study 015 (181 subjects without a histopathological truth standard)

Reader	Specificity (%)	(95% CI)
1	100	(98,100)
2	68	(61,75)
3	99	(97,100)
4	99	(97,100)
5	99	(96,100)

Thus, although the specificity data are not as strong as the results of sensitivity tests, but overall the evidence does support approval of flutemetamol.

IMAGING REPRODUCIBILITY AND READER AGREEMENT

Imaging reading reproducibility and agreement between readers were tested in Study 021. As shown in Table 2 of Dr. Marzella's review (Table on Page 9 of Dr. Ye's review), overall Fleiss' kappa for inter-reader reproducibility was 0.83 (95% CI 0.79 to 0.86), which met the pre-specified success criterion (95% CI lower bound >0.60). Reproducibility analyses were also consistent for different subset of Study 021 and met success criteria except for two small subsets with 10 or fewer patients. Intra-reader reproducibility in the same study was also acceptable (see discussion on Page 8 of Dr. Ye's review). Support of inter-reader reproducibility from Study 015 was weaker for potential reader bias, as noted by Dr. Davis (page 36), and probably not needed.

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READING METHOD AND READER'S TRAINING PROGRAM

As noted by Dr. Marzella, practical reading method and effective training program for readers are integral parts of requirements for approval of imaging agents. For flutemetamol, the reading method developed by this NDA applicant is described in relatively details in Dr. Ye's review (Page 10), which appears to be practical.

The effectiveness of the Electronic Self Training developed by the applicant was evaluated in Study 021 and the performance of thus trained readers was similar to that of in-person training (Study 007), as shown below comparing two panel of readers in Studies 007 and 021:

Test Performance		In person training (Study 007)	Electronic Self-training (Study 021)
Sensitivity (%)	median	88	93
	range	81-93	86-93
Specificity (%)	median	88	84
	range	44-92	60-92

INTERPRETATION OF IMAGING DATA AND APPLICATION IN CLINICAL SETTING

As noted above, collecting histopathological data from subjects who are true negative for amyloid plaques in the brain is difficult because biopsy or autopsy in such groups is either unethical or impractical. On the other hand, imaging studies in subjects who will likely consent to histopathological sampling tend to enroll patient populations skewed towards more advanced disease, not representative of general population who may need the imaging study. A less serious concern about such studies is the variation in interval between imaging studies and the post-mortem examinations.

The reviewers also noted that the imaging studies were conducted without access to the clinical information for the investigators, both the imaging readers and pathological examiners. Such setting is not realistic and raises the question whether the results are applicable to clinical practice.

The above limitations in interpretation of clinical study data are due to the protocol design to facilitate recruitment of subjects with higher event rates (thus smaller sample size) and to minimize investigators' bias. It is a compromise between reality and the necessity to improve the efficiency and productivity of clinical development. They do not affect the approvability of this application.

As described above, specificity data are not as robust as that of sensitivity. Since only negative scan rules out Alzheimer's disease, false negative scan (i.e. low sensitivity) is clinically consequential and undesirable. On the other hand, positive scans do not rule any conditions nor preclude further diagnostic work-up. Thus one may argue that false positive reading of the imaging data carries a less serious impact on the patient management. This clinical consideration makes the specificity results less critical for approval.

Lastly, the correlations of amyloid imaging findings with the diagnosis, prognosis & response to treatment of Alzheimer's disease have not been investigated. This should be reflected in the proposed labeling. Another related but unanswered question about the clinical usefulness of detecting amyloid plaques by imaging studies is, at the current state of technology,

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how much the clinicians rely on such imaging data in their overall management of patients with Alzheimer's disease.

SAFETY

Flutemetamol was positive for mutagenicity in in vitro assays (Ames and mouse lymphoma) but was negative in *in vivo* assays. I agree with Dr. Marzella and other reviewers that this finding does not raise a safety concern because of the proposed single micro-dose use. The results are described in the package insert. In the clinical studies, the medical reviewers' assessment that two deaths and two other cases of non-fatal serious adverse events are not drug related is concurred. A rare case of hypersensitivity reaction did occur in the clinical trials; how to manage such risk has been proposed in the labeling. Administration of flutemetamol was discontinued for a few patients who experienced reactions (chest discomfort, dyspnea etc.) that resolved spontaneously and promptly upon withdrawal. Other adverse reactions were also rare, reversible and well-tolerated (see medical reviews).

OTHER REGULATORY ISSUES

Use of flutemetamol in pediatric patients is considered unlikely. A full waiver for PREA related studies was granted.

BENEFIT/RISK

As summarized above, the effectiveness of flutemetamol in detecting amyloid plaques is well-supported by the results of the imaging studies. While the data supporting specificity were not as robust as that of sensitivity, there is no doubt about the overall efficacy of flutemetamol. Limitations in the interpretation and applicability of the clinical data are recognized, but they do not preclude its usefulness as an imaging agent in detecting the amyloid plaques in the practical clinical settings.

The risks of using flutemetamol according to the labeling instructions involve mainly exposure to radiation and incorrect reading of the imaging studies, which are comparable to similar imaging agents. Other adverse events were mostly manageable. Overall the risks are justifiable by the potential benefits.

CONCLUSIONS

It is recommended that Flutemetamol F 18 be approved as a new imaging agent for detection of amyloid plaques in the brain.

CC:
ORIG: NDA- 203137
Director, ODE-IV
Director, DMIP
Review team of NDA-203137

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APPEARS THIS WAY ON ORIGINAL

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/s/

SHAW T CHEN
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