CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203137Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	9/16/2013
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA # **Supplement #**	203137 0
Applicant Name	GE Healthcare
Date of Submission	10/26/2012
PDUFA Goal Date	10/26/2013
Proprietary Name / **Established (USAN) Name**	Vizamyl Flutemetamol F 18
Dosage Forms / Strength	Solution for Injection 150 MBq/ml 5mCi/ml
Proposed Indication(s)	Vizamyl is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions, as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations. Limitations of Use: • A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder • Safety and effectiveness of Vizamyl have not been established for: o Predicting development of dementia or other neurological condition o Monitoring responses to therapies
Action/Recommended Action for NME:	Approval Yes

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Phillip B Davis M.D.
Statistical Review	Lan Huang Ph.D.
Pharmacology Toxicology Review	Sally J Hargus Ph.D.
CMC Review	Ravindra K Kasliwal Ph.D.
Microbiology Review	Robert J Mello Ph.D.
Clinical Pharmacology Review	Christy S John Ph.D.
OPDP	Adora Ndu
OSI	Jong Hoon Lee M.D.
CDTL Review	Brenda Ye M.D.
OSE/DMEPA	Kevin Wright Pharm. D.
OSE/DRISK	Joyce Weaver Pharm. D.

OND=Office of New Drugs
OPDP Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI= Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Flutemetamol F 18 (Vizamyl), is a radioactive diagnostic agents proposed for use for Positron Emission Tomography imaging of the brain for visualization of β amyloid plaque. The regulatory pathway that was followed in the development of flutemetamol F 18 is similar to the pathway used for florbetapir F 18 (Amyvid) another radiopharmaceutical approved for use in PET imaging of the brain to visualize β amyloid plaque.

The development of these imaging agents rests on the notion that the detection of β amyloid in brain scans can provide clinically useful information. The presence of β amyloid plaque detected histologically in the brain at post-mortem is one of the characteristics of Alzheimer's disease. Therefore a PET scan that is negative for β amyloid is useful because it decreases the probability that a patient with impaired cognition has Alzheimer's disease. However β amyloid plaques in the brain are also present in other neurodegenerative diseases and in the elderly. For this reason a PET scan that is positive for β amyloid is not useful for making a clinical diagnosis of Alzheimer's disease.

Proof of concept studies for β amyloid imaging agents typically include *in vitro* binding studies of post-mortem human brain homogenates containing fibrillar amyloid. These studies estimate the dissociation constant of the investigational imaging agent. Additional studies evaluate the co-localization of radiolabeled imaging agent and stains or antibodies to β amyloid in post-mortem brain sections. The efficacy trials of the β amyloid imaging agents have two main objectives. The trials are designed to demonstrate that the performance

(sensitivity and specificity) and the reproducibility of the image interpretation methods are acceptable.

The first clinical study objective, assessment of the performance of β amyloid imaging agents requires single-arm studies in terminally ill patients with and without a cognitive disorder who consent to undergo a post-mortem examination of the brain. These studies are designed to compare β amyloid burden in virtual brain slices from PET scans and β amyloid burden in post-mortem brain sections examined histopathologically. The limitations of these studies include low accrual, variable interval between in life and post-mortem assessments, and a patient population skewed towards more advanced disease.

The PET images are randomized and are interpreted independently by multiple trained radiologists (readers) who are blinded to clinical information. Generally the readers perform a qualitative assessment of β amyloid burden in specific brain regions and make a final binary interpretation of the scan as either positive or negative. Negative scans generally show more radioactivity signal in the white matter than in the gray matter resulting in visualization of distinct grey-white contrast. Positive scans show loss of grey-white contrast and/or increased cortical gray matter signal.

The brain histology is assessed centrally in a standardized manner by experienced pathologists who are blinded to the interpretation of the PET scans. These standard procedures generally minimize variability of the interpretations and enhance the verifiability of the reading process. Using histopathology as the truth standard the sensitivity and specificity of the PET scan interpretations can be assessed.

The second clinical study objective, assessment of reproducibility of image interpretations requires the development of a clinically applicable reading method and training procedure. For this testing subjects without cognitive impairment (e.g. healthy young volunteers), mild cognitive impairment (MCI) or dementia receive a radiopharmaceutical injection and are scanned. These studies are designed to assess inter- and intra-reader concordance in image interpretation across a range of cognitive dysfunction. Reader performance in patients with a truth standard (post-mortem) is also determined. Given the importance of image reproducibility, it is generally recommended that in clinical use readers successfully complete an electronic-based training program developed and provided by the manufacturer.

Studies have not been carried out to determine whether or not β amyloid imaging agents can be used as prognostic tools to determine the likelihood of progression of cognitive decline or to predict response to treatment for dementia. These are important limitation in the uses of these agents.

A full discussion of the study designs and endpoints for this product class can be obtained from the meeting materials and transcripts of the Peripheral and Central Nervous System Advisory Committee meetings held on October 23, 2008 and on January 20, 2011.

2. Background

Alzheimer's disease is a chronic neurodegenerative disorder with β amyloid accumulation in the brain as a disease hallmark. Amyloid is an abnormal extracellular aggregate of insoluble protein fibrils in body tissues or organs. It has a β pleated sheet pattern on X-ray diffraction analysis, and staining properties that are used for histopathologic diagnosis. Alzheimer's disease usually manifests in middle or late life with progressive development of cognitive dysfunction such as memory loss, language difficulty, executive dysfunction, psychiatric and behavioral symptoms, and difficulty performing activities of daily living. Alzheimer's disease has important public health implications; its prevalence increases with age and it's estimated that it affects 12% of persons in the U.S. greater than 65 years of age. A clinical diagnosis of Alzheimer's disease may be aided by laboratory testing including imaging; however a definitive diagnosis can only be made by pathological evaluation of brain at post-mortem.

Pharmacology proof of concept studies show that flutemetamol F 18 binds to β-amyloid plaques in brain slices and to fibrillar β amyloid in human brain homogenates. The F-18 isotope produces a positron signal that is detected by a PET scanner. Following intravenous injection flutemetamol F 18 diffuses into the brain. Over time, the blood flow reduces overall brain flutemetamol F 18 signal with differential retention of the signal in cortical areas that contain β amyloid aggregates. Differences in signal intensity between brain regions form the basis of image interpretation methodology. Stable signal begins approximately 30 minutes after flutemetamol F 18 injection and persists for at least 120 minutes.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer Dr. Ravindra Kasliwal regarding the acceptability of the manufacturing of the drug product and drug substance. The reviewer determined that the NDA contains sufficient information to ensure the identity, strength, quality and purity of the drug substance, final intermediate and drug product. There are no outstanding issues with specifications methods or impurities. Manufacturing site inspections were acceptable. Stability testing supports an expiration dating period of 10 hours.

I concur with the conclusions reached by the clinical microbiology reviewer Dr. Robert Mello that there are no outstanding clinical microbiology or sterility issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer Dr. Sally Hargus that there are no outstanding issues that preclude approval. Dr Hargus concluded that the safety pharmacology studies identified no safety signals and the results of the toxicology studies supported the proposed clinical mass dose of 20 μg of flutemetamol. Flutemetamol was positive for mutagenicity in *in vitro* assays (Ames and mouse lymphoma) but was negative in

in vivo assays. The results are cited in the package insert. I agree that this finding does not raise a safety concern because of the proposed single microdose use.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer Dr. Christy John that there are no outstanding clinical pharmacology issues that preclude approval. Dr. John concluded that the recommended radioactive dose (5mCi) chosen to maximize signal to noise ration in the brain is as low as reasonably achievable.

6. Clinical Microbiology

This section is not applicable to this application. No clinical microbiology data were included in the submission.

7. Clinical/Statistical-Efficacy

I concur with the assessments of the clinical reviewer Dr. Phillip Davis and the statistical reviewer Dr. Lan Huang that the efficacy studies of Vizamyl have met their objectives. The findings and conclusions by the reviewers are summarized below.

Studies GE067-007 and GE067-021 are considered confirmatory. The clinical reviewer found that the reading methodology developed by the sponsor and the electronic self-training program are of acceptable quality and are adequately described in the final labeling. The blinded imaging evaluation methods used to determine the performance characteristics of Vizamyl were considered adequate to minimize bias, ensure independence of the interpretations and to provide an assessment of the reproducibility of the interpretations.

As for the truth standard, sections of brain at post-mortem were evaluated using CERAD criteria to determine β amyloid plaque density and to establish if a patient met pathologic criteria for a diagnosis of Alzheimer's disease. The methodology for the processing and blinded consensus evaluation of the brain sections was sound.

Study GE067-007. This was a prospective, open-label, single-arm study designed to evaluate the diagnostic performance (sensitivity as primary analysis, specificity as secondary analysis) of Vizamyl PET imaging for detecting β amyloid in the brain. Patients 55 years of age or older who were diagnosed with terminal illnesses and had a life expectancy of less than 1 year were studied. The patients were scanned and were followed until death or the end of the study.

Of the 180 patients scanned, 68 died during the study and were evaluable at post-mortem. The clinical diagnoses of cognitive disorders among the evaluable patients were as follows: 30 (44%) with Alzheimer's disease,17 (25%) with other cognitive disorders, and 21 (31%) with

no cognitive impairment. Vizamyl PET images were presented in a random order to five readers who were blinded to clinical information, received in-person training and interpreted the images independently.

The clinical reviewer determined that the Vizamyl performance characteristics are clinically acceptable. The statistical reviewer verified the Vizamyl test performance characteristics. Study 007 achieved its primary efficacy objective because the lower bound of the 95% confidence limit for sensitivity exceeded 70% for at least 3 of the 5 readers. The point estimates (95% CI) for specificity were 88% (69%, 98%), 92% (74%, 99%), 44% (24%, 65%), 80% (59%, 93%), and 92% (74%, 99%) for the 5 readers.

In conclusion Study 007 validates the visual assessment of brain amyloid plaque density using Vizamyl images by comparing it to truth standard of histopathology assessment of amyloid density in brain at post-mortem. The clinical reviewer notes that the patient population for whom a truth standard is available (terminally ill) is not quite representative of the indicated population. Study 021 addresses this issue by assessing brain β amyloid density in images from subjects with a range of cognitive functions.

Study GE067-021. This was a prospective study designed to achieve several important objectives including confirmation of the sensitivity and specificity of Vizamyl PET image interpretation using an electronic-based self-training method (more clinically applicable). Another important objective was the evaluation of the inter-reader and intra-reader reproducibility of Vizamyl PET image interpretation from subjects with a range of cognitive function and for whom a truth standard might not be obtainable.

Study 021 enrolled no new subjects and relied on images of subjects who had participated in previous studies. Inter-reader reproducibility was assessed from subjects with a truth standard (68 from post-mortem and 36 from a brain biopsy) and without a truth standard (28 cognitively normal elderly, 31 young healthy, 80 with mild cognitive impairment, and 33 with probable AD. Intra-reader reproducibility was assessed from 29 images.

Study 021 was to be considered successful if the null hypothesis for both sensitivity and specificity was rejected for each of 3 of the 5 blinded readers. The lower bounds of the two-sided 95% CIs for sensitivity and specificity would be >70%. The criterion for success of inter-reader agreement would be that the lower bound of the 95% CI for kappa exceeds 0.6

Study 021 achieved both its primary and secondary objectives. Table 1 shows the median and the range of values for sensitivity and specificity across the five readers. Table 1 also provides a comparison of sensitivity and specificity for the in-person and self-training method for the same images (n=68) for which the truth standard is available. The performance characteristics are similar providing support for the clinical applicability of the image interpretation using self-training methods.

Table 1. Sensitivity and Specificity (in %) of Vizamyl Image Interpretation by Reader Training Method among Patients with Post-mortem Truth Standard

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

* range among five independent blinded readers

Study 021 also achieved its objective of demonstrating the reproducibility of the scan results. Table 2 shows that for blinded visual interpretations of PET images (N=276), inter-reader agreement across all 5 readers was 81%, with a kappa value of 0.83 (95% CI 0.79, 0.86).

Inter-reader agreement met the secondary success criterion, which required the lower bound of the 2-sided CI for kappa to exceed 0.6. Intra-reader agreement ranged from 93% to 100% among the five blinded readers.

Table 2 Study 021. Median Number of Positive Vizamyl Scans and Reproducibility of Scan Results

Subject Group by Cognitive and Truth Standard (TS)	Positive Scans N[a]	Kappa (95% CI)	Percent of Scans with Inter-reader Agreement		
			3 of 5 readers agreed	4 of 5 readers agreed	5 of 5 readers agreed
All 276 study subjects	139	0.83 (0.79, 0.86)	5	14	81
All subjects with a TS, n=104 (68 post-mortem; 36 biopsy)	58	0.74 (0.68, 0.80)	6	24	70
All subjects without a TS, n = 172	76	0.88 (0.83, 0.92)	5	8	87
pAD, n = 63 (30 with TS[b]; 33 no TS)	47	0.88 (0.80, 0.96)	3	6	90
aMCI, n = 80 (0 with TS)	45	0.89 (0.82, 0.96)	4	7	89
Elderly cognitively normal without TS, n = 28	2	0.46 (0.34, 0.57)	4	14	82
Cognitively normal with TS[c], (n=21)	10	0.64 (0.5, 0.77)	5	38	57
Other (non-AD) dementia with TS, n=53[d]	27	0.71 (0.63, 0.80)	8	25	68

[a] median number of scans interpreted as positive across the 5 readers for each group of subjects
[b] 30 with a post-mortem truth standard
[c] all 21 with a post mortem truth standard
[d] 17 from autopsy, 36 from biopsy of which 5 were not definitively classified as pAD based on clinical diagnosis

pAD: probable AD; aMCI: amnestic MCI; Elderly: 55 years or above

Examination of the level of agreement across readers in various subgroups of images including patients with and without truth standard does not raise concerns about reproducibility of the image interpretation in the subgroups.

In conclusion the efficacy studies support the intended use of Vizamyl as a qualitative assessment of beta amyloid plaque density. Vizamyl is not intended for use as a diagnostic agent. A positive scan does not establish a diagnosis of Alzheimer's disease or any other cognitive disorder. The intended use of Vizamyl is consistent with a "functional,

physiological, or biochemical assessment" as described in the 2004 FDA Guidance for Industry: Developing Medical Imaging Products Part 2: Clinical Indications.

8. Safety

I concur with the clinical reviewer's assessment that the size of the database and the clinical assessments performed are adequate to evaluate the safety of flutemetamol F 18 and that there are no safety concerns that preclude approval of the drug for its intended use.

Of the 761 adults studied nearly all received a single intravenous injection of flutemetamol F 18 and underwent a PET scan. The median radioactive dose was 5 mCi and the mass dose was 20 micrograms. The study population ranged from healthy adults to terminally ill patients and included patients with dementia, amnestic mild cognitive impairment (a MCI), and normal pressure hydrocephalus. No pharmacologic effects were expected and none were observed.

The clinical reviewer determined that one patient developed a serious hypersensitivity reaction characterized as flushing, shortness of breath, and chest pressure one minute after receiving flutemetamol F18 and was treated with one dose of epinephrine. Four other serious events including two fatalities temporally associated with flutemetamol F-18 were judged to be unrelated to the drug. The risk of hypersensitivity reactions is described in the *Warnings and Precautions* section of the prescribing information.

Flutemetamol increases a patient's cumulative exposure to radiation. The risk of radiation exposure is mentioned in the *Warnings and Precautions* section of the prescribing information

Reliability of image interpretation is an important concern with the use of beta amyloid imaging agents. Proficiency of interpretation in clinical practice is accomplished through the successful completion of an electronic self-training program developed by the manufacturer and cited in the labeling. Validation of the training program is an important consideration in the development of beta amyloid imaging agents. In addition errors in interpretation are evident from the flutemetamol F 18 performance data in the clinical trials. To highlight the importance of training and the limitations of visual estimation of β amyloid plaque density, the potential for error in interpretation of the PET imaging is described as a risk in the *Warnings and Precautions* section of the prescribing information.

The Division of Pharmacovigilance II reviewers (M E Kieffer Pharm. D. and JM Tonning M.D.) conducted a search and evaluation of FDA's Adverse Event Reporting System (FAERS) for domestic and foreign reports for diagnostic radiopharmaceuticals in general and for the marketed amyloid imaging agent florbetapir F 18. The reviewers identified no emerging safety concerns.

With regard to the Risk Evaluation and Mitigation Strategy (REMS), the FDA risk management analyst Dr. Weaver determined that there are no safety concerns for flutemetamol

F 18 requiring a REMS. Product labeling alone is sufficient to communicate the risks associated with the use of the drug. I concur with this assessment.

9. Advisory Committee Meeting

No advisory committee meeting was held. The clinical trial designs and efficacy endpoints for radiopharmaceutical imaging drugs that target βamyloid were established at meetings of the Peripheral and Central Nervous System Drugs Advisory Committee held on October 23, 2008 and on January 20, 2011. The Applicant followed this established regulatory path for the efficacy studies of flutemetamol F 18.

10. Pediatrics

The FDA's Pediatric Review Committee granted a full waiver of the required pediatric assessment of flutemetamol F 18 under the Pediatric Equity Research Act because the accumulation of β amyloid and development of Alzheimer's disease do not affect any pediatric population.

The Pediatric and Maternal Health Staff provided advice on the relevant specific population sections of the prescribing information for flutemetamol F 18.

11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues with the flutemetamol F 18 application.

The regulatory approach to product development for amyloid imaging agents was established at FDA advisory committee meetings in 2008 and 2011. Important agreements on the clinical development plan for flutemetamol F 18 were reached at meetings between FDA and the Sponsor in March 2009 and September 2010.

Submission quality and integrity and compliance with good clinical practice were verified by FDA audits. The FDA Office of Scientific Investigations reviewer (Dr. JH Lee) summarized the results of the clinical inspections and determined that overall study data appeared reliable and minor observed deficiencies were unlikely to affect the studies' outcomes. I concur with that assessment.

The clinical inspection verified the Sponsor's compliance with GCP regulations, study protocols and standard operating procedures particularly with respect to image interpretation, histopathology truth standard, electronic data controls and test article accountability. The inspection of the central imaging laboratory for study GE-067-021 identified no important

deficiencies. The inspection verified compliance with good clinical practice regulations, standard operating procedures for the laboratory and protocol. The inspection audited 345 case report forms from 32 study subjects evaluated by 5 independent readers. One data error was identified; 1 of 160 reader decisions was recorded as abnormal in CRF and normal in the NDA listing. Overall the data was considered reliable and the classification of the inspection was no action indicated.

Audits of the image interpretation process for studies GE-067-007 and GE-067-015 Revealed no unblinding or biased image interpretation; the efficacy data in the NDA were verified against a sample of the corresponding CRF. An audit of the central histopathology laboratory confirmed integrity of study blind and verified the truth standard for the 68 patients who underwent post-mortem examination. Audit of data management and statistical programming identified no deficiencies.

The clinical reviewer did not identify ethical concerns with the conduct of the studies. A total of three among all of the studies' investigators reported financial interests. There was no evidence of effects by these interests on data integrity and no likelihood of an impact on study outcomes.

The FDA DMEPA reviewer (Dr. K. Wright) found the proposed proprietary name to be acceptable from a safety and promotional perspective. I concur with that assessment.

The FDA's Office of Prescription Drug Promotion reviewer (A Ndu) evaluated the flutemetamol F 18 labeling from the promotional perspective. The reviewer recommended rephrasing or omission of specific statements or claims in the Prescribing Information and these recommendations were adopted in the final version of the labeling.

With regard to Post-market Requirements and Commitments (PMC/PMR), I concur with the recommendation of the primary reviewers (clinical, clinical pharmacology, and drug safety) that no PMC or PMR are necessary.

12. Labeling

There are no outstanding labeling issues.

The proprietary name Vizamyl is acceptable. Final prescribing information, carton and immediate container labels have been finalized. Patient labeling and medication guide are not needed and none were considered.

13. Decision/Action/Risk Benefit Assessment

I concur with the recommendation made by the FDA primary and secondary reviewers in chemistry, microbiology, pharmacology toxicology, clinical pharmacology, clinical, and statistics, that this application be approved.

I conclude that Vizamyl has an acceptable risk benefit profile.

With regard to efficacy, the qualitative visual assessment of amyloid density in Vizamyl PET images provides useful information because a negative scan is inconsistent with a neuropathologic diagnosis of AD. On the other hand a positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder, and in addition the prognostic or predictive value has not been established; the labeling highlights these limitations.

With regard to safety, the risk of hypersensitivity reactions to Vizamyl has been noted. The administered radioactive dose of flutemetamol F18 is acceptable, but it increases a patient's cumulative exposure to radiation. Finally reliability of image interpretation is an important concern with the use of beta amyloid imaging agents. Proficiency of interpretation in clinical practice is to be accomplished through the successful completion of an electronic self-training program. The labeling describes these issues in the Warnings and Precaution section.

No REMS, PMC or PMR are needed and none were considered.

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/s/

LIBERO L MARZELLA
09/16/2013