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RESEARCH**

APPLICATION NUMBER:

203137Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2013
From	Brenda Ye MD
Subject	Cross-Discipline Team Leader Review
NDA	203137
Applicant	GE Healthcare
Date of Submission	October 26, 2012
PDUFA Goal Date	October 26, 2013
Proprietary Name / Established (USAN) names	Vizamyl/ flutemetamol F 18
Dosage forms / Strength	Solution for injection 150 MBq/ml, 5mCi/ml
Proposed Indication(s)	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
Recommended:	Approval

1. Introduction

The applicant of this NDA, GE Healthcare, submitted an NDA for Flutemetamol F 18 with the following proposed indication:



2. Background

The following is the product regulatory history. The clinical development paradigm for beta amyloid imaging agents was developed at advisory committee meetings and was generally followed by the Applicant.

2008 May 19: Pre-IND meeting

2008 Oct 23: Advisory Committee meeting. Please see the summary review for Amyvid at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202008Orig1s000SumR.pdf for an overview of the 2008 Advisory Committee meeting on developing amyloid imaging agents.

2009 Mar 26: Type C meeting to discuss clinical development plan.

2010 Sep 7: End of Phase 2 meeting to discuss clinical development plan, which would include an electronic training program for image interpretation.

2011 Jan 20: Advisory Committee meeting to discuss approval considerations of Amyvid

2012 Apr 12: Pre-NDA meeting to discuss NDA submission documentation.

3. CMC/Device

The FDA CMC reviewer Dr. Kasliwal determined that sufficient information is provided in the NDA, to ensure the identity, strength, quality, and purity of the drug product. The CMC reviewer also determined that there are no product quality microbiology issues and there are no outstanding issues with specifications, methods and impurities. Finally Dr. Kasliwal determined that the stability of the product has been sufficiently demonstrated to support a 10 hour expiration dating period. The microbiology reviewer Dr. Mello determined that the product microbiological quality is acceptable Therefore the reviewers recommended an approval action.

4. Nonclinical Pharmacology/Toxicology

The FDA Pharmacology/Toxicology reviewer Dr. Sally Hargus determined that the pharmacology proof-of-concept studies supported using flutemetamol to target and bind to β amyloid deposits in brain. The reviewer determined that the safety pharmacology studies

identified no safety signals and the results of the toxicology studies supported the proposed clinical dose of 20 µg of flutemetamol.

Dr. Hargus determined that the results from all of the in vivo–based genotoxicity assays of Flutemetamol were negative. However, the results of in vitro assays (bacterial mutagenicity and mouse lymphoma assay) with Flutemetamol were positive. The sponsor conducted studies that support the hypothesis that only in the presence of an exogenous activating system (Aroclor-induced rat S9 fractions) are mutagenic metabolite(s) of flutemetamol produced. The reviewer concluded that the positive result is unlikely to be a safety issue for a microdose of a diagnostic imaging agent.

Reproductive and developmental toxicity studies were not required or conducted based on the results of the rat and dog toxicity studies, the microdose of flutemetamol administered for a single PET evaluation, and the proposed population of adult patients with suspected AD or other dementia. Carcinogenicity studies are not required for radioactive diagnostic imaging agents, and therefore, were not conducted. Based on these findings Dr. Hargus recommended approval of the NDA.

5. Clinical Pharmacology/Biopharmaceutics

The FDA Clinical Pharmacology reviewer Dr. Christy John determined that the selected dose is likely as low as reasonably achievable (ALARA). A clinical dose of 185 MBq (5 mCi) was chosen based on sufficient radioactivity in brain and target to non-target ratio in brain. No additional exposure-response relationship was determined for this single administration drug given as a microdose. A clinically significant effect of flutemetamol on QT/QTc prolongation is not expected based on QTc-Fridericia data in 743 subjects. The applicant did not conduct formal drug-interaction studies; however use of AD medication is not associated with a significant difference in SUVR. The reviewer recommended an approval action.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

The clinical development program included eleven studies, eight of which are considered Phase 3 by the sponsor. The two of the Phase 3 trials which serve as primary support for approval of NDA 203137 (Study 007 and Study 021) will be described in this review. Both studies were single arm and subjects underwent a Vizamyl injection and PET scan. The images were interpreted by five independent readers masked to all clinical information. PET images were reviewed first without, and subsequently with, brain CT or MRI images

Study 007. The results of this trial, in which whole-brain histopathology was used as the standard of truth to evaluate the performance characteristics of flutemetamol F 18, support approval of NDA 203137. Screening criteria required that subjects were 55 years of age or older and diagnosed with a terminal illness with a life expectancy of one year or less as estimated by the investigator.

Pre-mortem Vizamyl PET image interpretations from terminally ill patients were compared to post-mortem truth standard assessments of cerebral cortical neuritic plaque density in patients who died during the study. Subjects underwent anatomic brain imaging (typically computed tomography (CT)) followed by a 5 to 10 mCi Flutemetamol F 18 injection and a 30-minute PET scan starting approximately 90 minutes after injection of the study drug. Readers evaluated images using a clinically applicable binary image interpretation method (positive/negative) that involved evaluating regional Vizamyl brain uptake to yield a final overall image assessment that was compared to the truth standard. Before image interpretation, all readers underwent in-person tutoring on image interpretation.

For purposes of determining the agreement between the in-vivo Vizamyl image results and the post-mortem whole brain amyloid neuritic plaque density, Vizamyl results (negative/positive) were pre-specified to correspond with specific global histopathology plaque density scores, based upon a modification of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria, which use neuritic plaque counts as a necessary pathological feature of AD. Plaques were counted on slides with modified Bielschowsky silver stained tissue sections. The global brain neuritic plaque density score for each subject was determined by averaging across the scores (0-3) for five grey matter fields per slide and then across the six slides for each of eight regions; if any one region had a regional score of greater than 1.5 (midpoint between score of 1 (sparse) and 2 (moderate)), the subject's brain was classified as positive for amyloid.

Vizamyl Image Result	CERAD Classification (Score)	Neuritic Plaque Counts
Negative	None (0)	0
	Sparse (1)	1 to 5
Positive	Moderate (2)	6 to 19
	Frequent (3)	≥ 20

Of the 203 subject enrolled, 180 subjects were administered Vizamyl, 176 underwent PET scans, and 68 subjects underwent autopsy for the study. The median age was 82 years (range 47 to 98 years) and 57% of the patients were female. Forty-four patients had no cognitive impairment, 135 had dementia, no patients had mild cognitive impairment (MCI), and one patient had memory loss of unspecified nature. Sixty-nine patients died during the study; 68 had cerebral cortical amyloid status determined (43 positive and 25 negative) and were included in the primary analysis. The time interval between the Vizamyl scan and death ranged from 0 to 13 months, with a median of 2.7 months, and was less than one year for 66 patients and between 12 to 13 months for 2 patients. At autopsy, the global brain neuritic plaque density CERAD category was: frequent n=19; moderate n=22; sparse n=14; and none n=12.

Study 007 met the protocol-specified primary endpoint. The primary objective was to determine sensitivity of the blinded visual interpretation of PET images for detecting brain fibrillar β amyloid without the aid of anatomic images for each of five independent readers (point estimate and 95 % confidence interval). Success on the primary endpoint was achieved if the lower bound of the two-sided 95% confidence limit for sensitivity was greater than 70% for at least three of the five readers. Specificity of the blinded visual image interpretations without anatomic images was a secondary endpoint.

Study 007 (n=68)		
Reader	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
1	81 (67, 92)	88 (69, 98)
2	88 (74, 96)	92 (74, 99)
3	93 (81, 99)	44 (24, 65)
4	93 (81, 99)	80 (59, 93)
5	88 (75, 96)	92 (74, 99)

The median sensitivity and specificity, and range among the five readers, are summarized below.

Test Performance Study 007		
Sensitivity (%)	Median	88
	Range among the 5 readers	(81 – 93)
Specificity (%)	Median	88
	Range among the 5 readers	(44 – 92)

Of the 68 subjects who underwent autopsy, 43 were positive and 25 were negative based on histopathology. The median (and range) of correct read results, false negatives, and false positives were 59 (51 to 61), 3 (3 to 8), 3 (2 to 14), respectively.

		Study 007 Scan Results by Reader				
		1	2	3	4	5
All scans with autopsies (n = 68)	Correct	57	60	51	59	61
	False Positive	3	2	14	5	2
	False Negative	8	5	3	3	5

Study 021. The results of this trial, which evaluated the effectiveness of an electronic training program for Vizamyl image orientation and interpretation across 276 subjects with a broad spectrum of cognitive abilities who participated in earlier studies, also support approval of NDA 203137.

Of the 135 subjects the sponsor considers as having a truth standard,

- 68 subjects underwent autopsy in Study 007 and
- 36 patients with known or suspected normal pressure hydrocephalus underwent brain biopsy in three previous studies (009, 010, and 011).
- The analyses in this review do not consider the presumed negative β amyloid status for the 31 young healthy volunteers (40 years or younger) from a previous study (015) as a truth standard.

Of the 141 subjects which the sponsor considers as not having a truth standard,

- 60 subjects were from the Phase 3 amnesic mild cognitive impairment (aMCI)-to-AD conversion study (Study 005),
- 55 subjects were from the Phase 2 study ALZ 201,
- 10 subjects were from the European Phase 1 study ALZ 103, and
- 16 subjects were from the Japanese Phase 1 study (Study 014).

This review considers 104 subjects as having a truth standard (135 minus 31 young healthy volunteers) and 172 subjects as not having a truth standard (141 plus 31 young healthy volunteers).

Inter-reader reproducibility of image interpretation was assessed using images from subjects with a truth standard (68 patients who underwent an autopsy and 36 known or suspected normal pressure hydrocephalus patients with in vivo brain biopsy) and without a truth standard (28 cognitively normal volunteers 55 years or above, 80 patients with amnesic mild cognitive impairment (aMCI), 33 subjects with probable AD (pAD)), and 31 young healthy volunteers. Additionally, intra-reader reproducibility was assessed from 29 images (10%). Among the 276 subjects, the median age was 72 years (range 20 to 95), 136 were females, and 251 were Caucasian.

Study 021 met the protocol-specified primary endpoint. Success on the primary endpoint was achieved if the lower bound of the two-sided 95% confidence limit for sensitivity and specificity was greater than 70% for at least three of the five readers for the 135 subjects the sponsor considers to have a truth standard.

Study 021 (the subset of 135 subjects with a sponsor-defined truth standard)		
Reader	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
6	94 (84,99)	79 (68,87)
7	92 (81,98)	81 (71,89)
8	90 (79,97)	93 (85,97)
9	94 (84,99)	96 (90,99)
10	84 (71,93)	77 (67,86)

The following sensitivity analyses evaluating sensitivity and specificity for certain subsets were performed post-hoc and did not have pre-specified success criteria.

For the subset of 104 subjects with a histopathology truth standard, the lower bound of the 95% confidence interval was greater than 70% for all five readers for sensitivity. However, the lower bound of the 95% confidence interval was greater than 70% for only two of the five readers for specificity.

Study 021 Subset of 104 subjects with a histopathology truth standard		
Reader	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
6	94 (84,99)	68 (54,80)
7	92 (81,98)	79 (66,89)
8	90 (79,97)	89 (77,96)
9	94 (84,99)	72 (58,83)
10	84 (71,93)	94 (84,99)

For the subset of subjects who underwent autopsy, the lower bound of the 95% confidence interval was greater than 70% for all five readers for sensitivity. However, the lower bound of the 95% confidence interval was greater than 70% for only one of the five readers for specificity.

Study 021 Subset of 68 autopsy subjects		
Reader	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
6	93 (81,99)	72 (51,88)
7	93 (81,99)	84 (64,96)
8	91 (78,97)	88 (69,98)
9	93 (81,99)	60 (39,79)
10	86 (72,95)	92 (74,99)

The median sensitivity and specificity for the subset of subjects who underwent autopsy, and range among the five readers, are summarized below.

Study 021 (n=68) Test Performance		
Sensitivity (%)	Median	93
	Range among the 5 readers	(86 – 93)
Specificity (%)	Median	84
	Range among the 5 readers	(60 – 92)

The median (and range) of correct read results, false negatives, and false positives were 60 (55 to 61), 3 (3 to 6), 4 (2 to 10), respectively.

Image reproducibility for various subject groups in Study 021 is presented below. Inter-reader reproducibility analysis showed an overall Fleiss' kappa statistic of 0.83 (95% CI 0.79 to 0.86) which met the pre-specified success criterion (95% CI lower bound >0.60). Intra-reader reproducibility analysis showed that, between the two readings for each of the 29 duplicate patient images, one of the five readers had complete agreement for all 28 images, two readers had discordant reads for a single image, and three readers had discordant reads for two images. Intra-reader reproducibility for a sub-group of 8 images from aMCI patients showed that all five readers had complete agreement for all duplicate images.

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 subjects	139	0.83 (0.79,0.86)	5	14	81
All subjects with a TS, n=104 (68 autopsy; 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 (35 with TS ^b ; 28 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 Shown is the median number of scans interpreted as positive across the 5 readers for each subgroup of subjects listed in the first column.

^b 30 with TS from autopsy, 5 with TS from biopsy were not definitively classified as pAD based on clinical diagnosis

^c 21 with TS from autopsy, 0 with TS from biopsy

^d 17 from autopsy, 5 of 36 with TS from biopsy were not definitively classified as pAD based on clinical diagnosis

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

A negative PET scan result is clinically meaningful (reduces the likelihood of AD) whereas a positive scan result is less clinically meaningful (older people with normal cognition may have a positive scan).¹ One perspective is that sensitivity is more important than specificity on an individual patient level since the certainty of a negative result may provide reassurance that a change in cognitive status is not due to AD. Sensitivity appears stable across the subsets with a truth standard described above. A lower specificity (higher false positive rate) may deprive certain patients of reassurance that their cognitive impairment is not due to AD.

¹ October 23, 2008 Advisory Committee meeting <http://www.fda.gov/ohrms/dockets/ac/cder08.html#PeripheralCentralNervousSystem> and January 2011 Advisory Committee meeting <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm235846.htm>

Although the specificity for subjects with a histopathology truth standard and for subjects who underwent autopsy is lower for many of the readers than for the sponsor-defined primary efficacy population, it is worth noting that none of the subjects with a histopathology truth standard (autopsy or biopsy) are likely included in the intended population for amyloid imaging agents. Rather, the intended population likely comprises of patients with MCI for which no histopathology truth standard is readily obtainable. For MCI subjects, all five readers agreed on the binary interpretation of Vizamyl PET images for 89% of subjects.

PET image reading method. The objective of Vizamyl image interpretation is to provide an estimate of the brain β -amyloid neuritic plaque density, not to make a clinical diagnosis. Image interpretation is performed independently of a patient's clinical features and relies upon recognition of image features in certain brain regions.

The reading method developed by the sponsor of Vizamyl differs from that developed by the sponsor of the approved amyloid imaging agent, Amyvid. Whereas black and white images are used to interpret Amyvid scans, color images are used to interpret Vizamyl scans. The Vizamyl reading method, which focuses on several regions within the brain, is detailed below.

Image Orientation

Orient axial and coronal images to show symmetry of brain structures, with equal heights of structures bilaterally. Orient sagittal images so that the head and neck are neither flexed nor extended, and the eyes are facing straight ahead to the left or right; the anterior and posterior aspects of the corpus callosum should be parallel to the AC-PC line.

Image Display

- Display images with all planes (axial, sagittal and coronal planes) linked by crosshairs.
- Select a color scale that exhibits a continuous progression of low through high intensity (e.g., rainbow, spectrum, or Sokoloff scale). The selected color scale should (1) provide distinct colors that clearly discriminate intensity levels above and below the intensity level of the pons, (2) provide a distinct color for regions with little or no amyloid binding such as the cerebellar cortex, and (3) provide a range of at least five distinct colors above 50 to 60% of the peak intensity.
- Display the reference scale. Adjust the color scale to set the pons to approximately 90% maximum intensity. The cerebellar cortex should represent approximately 20-30% of peak intensity on both negative and positive Vizamyl scans.
- Briefly display axial brain slices from bottom to top and look for signs of atrophy.
- Systematically review the following brain regions (recommended plane) for Vizamyl uptake as described in *Image Interpretation* below:
 - Frontal lobes (axial, with optional sagittal plane display)
 - Posterior cingulate and precuneus (sagittal, with optional coronal plane display)
 - Lateral temporal lobes (axial, with optional coronal plane display)

- Inferolateral parietal lobes (coronal, with optional axial plane display)
- Striatum (axial, with optional sagittal plane display)

Image Interpretation

Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of the image assessment [*see Warnings and Precautions (5.2)*]. Images are designated as positive or negative by comparing the radioactivity in cortical grey matter with activity in adjacent white matter, or based on the intensity in the five regions mentioned above. The signal uptake in the cerebellum does not contribute to scan interpretation (for example, a positive scan may show retained cerebellar grey-white contrast even when the cortical grey-white contrast is lost).

- *Negative scans* show more radioactivity in white matter than in the grey matter, creating clear grey-white contrast. Specifically, a negative scan would have the following characteristics:
 - frontal, lateral temporal, inferolateral parietal lobes: gradual gradient from bright intensity of the white matter to lower intensity at the periphery of the brain; distinct sulci with concave surfaces (white matter sulcal pattern)

and

- posterior cingulate and precuneus: grey matter uptake below 50-60% of peak intensity; gap of lower intensity separates two hemispheres on coronal view

and

- striatum: approximately 50% of peak intensity in the region between the higher intensities of the thalamus and frontal white matter (striatal “gap”)
- *Positive scans* show at least one cortical region with reduction or loss of the normally distinct grey-white matter contrast. These scans have one or more regions with increased cortical grey matter signal (above 50-60% peak intensity) and/or reduced (or absent) grey-white matter contrast (white matter sulcal pattern is less distinct). A positive scan may have one or more regions in which grey matter radioactivity is as intense or exceeds the intensity in adjacent white matter.

Specifically, a positive scan would have the following characteristics:

- frontal, lateral temporal, or inferolateral parietal lobes: high intensity seen to the periphery of the brain, with sharp reduction of intensity at the brain margin; sulci not distinct due to fill-in by high intensity grey matter, resulting in a convex surface at the edge of the brain

or

- posterior cingulate and precuneus: grey matter uptake above 50-60% of peak intensity; high grey matter intensity that closes the gap between the two hemispheres on coronal view

or

- striatum: intensity above 50-60% of peak intensity; gap between thalamus and frontal white matter not distinct

If any one of the brain regions systematically reviewed for Vizamyl uptake (see *Image Display* above) is positive, then the scan is considered positive. Otherwise, the scan is considered negative.

Among patients with clinically important beta amyloid neuritic plaques in the brain, the temporal lobes, parietal lobes, and striatum may not be affected. Therefore, Vizamyl uptake in these regions may not be as intense as in the frontal lobes or the posterior cingulate and precuneus regions.

Atrophy, particularly in the frontal and inferolateral parietal lobes, may affect the interpretability of scans. For cases in which there is uncertainty as to the location of the grey matter on the PET scan, examine the striatum for Vizamyl uptake as it is less affected by atrophy than other regions of the brain. If the patient's MRI or CT brain images are available, the interpreter should examine the CT or MRI images to clarify the relationship between Vizamyl uptake and grey matter anatomy.

Other factors that may affect the ability to interpret Vizamyl images include patient factors such as brain pathology, surgical changes, post-radiation therapy changes, and implants. Some scans may be difficult to interpret due to image noise, patient malpositioning, or over-smoothing.

8. Safety

As a diagnostic radiopharmaceutical, Vizamyl harbors radiation risks and the risk associated with incorrect image interpretation. The radiation risk is similar to that for the currently marketed amyloid imaging agent, Amyvid, and for other currently marketed diagnostic radiopharmaceuticals. The reproducibility of the Vizamyl image interpretation methods is similar to that of Amyvid. A WARNING AND PRECAUTION has been added to the label regarding the risk of image misinterpretation and radiation risk (similar to text in the Amyvid label).

In clinical trials, 761 adults (367 men and 394 women, 91% Caucasian) with a mean age of 62 years (range 18 - 93 years) received Vizamyl. Most subjects (530, 70%) received a dose of Flutemetamol F 18 Injection from 166.5 to 203.5 MBq (185 MBq \pm 10%). Subjects who were unable to tolerate a 30-minute imaging session (154, 20%) received a dose from 333 to 407 MBq (370 MBq \pm 10%) to allow for shorter imaging times.

Deaths / Fatal Serious Adverse Events (SAEs). In Study 007 (“autopsy” study), two deaths occurred within the 24-hour follow up period. The cause of death was attributed to prostate cancer for one subject and senile dementia for the other subject. Neither death was considered related to Vizamyl, and this reviewer agrees based on the case summaries.

Non-fatal SAEs. Two subjects experienced non-fatal SAEs within thirty days of Vizamyl administration: anemia, change in mental status. Both subjects continued in the study. Neither was attributed to Vizamyl and this reviewer agrees based on the case summaries.

In the clinical trials, one subject experienced a serious hypersensitivity reaction with flushing, dyspnea and chest pressure within minutes following Vizamyl administration and recovered with treatment. Skin prick testing with flutemetamol F 18 injection, polysorbate 80, and ethanol was negative. Intradermal testing with polysorbate 80 was positive. A serum sample obtained 2.5 hours after symptom onset was tested for tryptase (enzyme released from mast cells) and interpreted as not ruling out an anaphylactic / anaphylactoid reaction. A serum sample obtained four weeks after the reaction demonstrated no IgE binding to derivatives of Flutemetamol F 18, flutemetamol, and polysorbate 80. The sponsor interprets these results as indicating that the reaction was not IgE-mediated and therefore an anaphylactoid reaction.

Polysorbate 80 was introduced during clinical development to improve solubility and handling (prevent loss of flutemetamol due to adsorption of flutemetamol to surfaces of dispensing equipment).

The sponsor managed the risk of hypersensitivity reaction to Flutemetamol F 18 during clinical development by excluding subjects with known or suspected hypersensitivity to any component of Flutemetamol F 18 Injection. The sponsor proposes to manage the risk after marketing by

- contraindicating use of Flutemetamol F 18 Injection in patients with known or suspected hypersensitivity to any component of the product;
- adding text to the Warnings and Precautions section of the label to advise users of the possibility of hypersensitivity, recommend immediate availability of emergency equipment and personnel trained in its use if a similar reaction occurs.

Most Frequent Adverse Events. Most adverse reactions were mild to moderate in intensity and resolved spontaneously. Among the 761 subjects, the most commonly reported adverse reactions (occurring in at least 1% of subjects) are shown below.

Adverse Reaction	N (percent of patients)
Flushing	16 (2%)
Blood pressure increased	10 (1%)
Headache	10 (1%)
Nausea	8 (1%)
Dizziness	8 (1%)

Dropouts and/or Discontinuations. Three subjects experienced treatment emergent adverse events (TEAEs) that led to discontinuation. The two subjects in whom the adverse events were considered related to Vizamyl experienced reactions that resolved within twelve minutes.

- chest discomfort, abdominal discomfort, arrhythmia, hypotonia
- dyspepsia, dyspnea, hypotonia

One subject experienced mild extravasation which was not considered related to Vizamyl.

Labeling. The safety risks posed by Vizamyl are cited in the Contraindications and Warnings and Precautions section of the labeling as follows.

CONTRAINDICATIONS. The agreed-upon text in section 4 is: Vizamyl is contraindicated in patients with a history of hypersensitivity reaction to Vizamyl, polysorbate 80, or any other inactive ingredient in Vizamyl [see Warnings and Precautions (5.1)].

WARNINGS AND PRECAUTIONS. The agreed-upon text in section 5 cites the risks of hypersensitivity, misinterpretation of scans and, radiation exposure.

Hypersensitivity Reactions

Hypersensitivity reactions such as flushing and dyspnea have been observed within minutes following Vizamyl administration. These reactions may occur in patients with no history of prior exposure to Vizamyl.

Before administering Vizamyl, ask patients about prior reactions to drugs, especially those containing polysorbate 80.

Have resuscitation equipment and trained personnel immediately available at the time of Vizamyl administration [see Contraindications (4)].

Risk for Image Misinterpretation and other Errors

Errors may occur while using Vizamyl PET images to estimate brain neuritic plaque density [see Clinical Studies (14)].

Image interpretation is performed independently of the patient's clinical information. The use of clinical information in the interpretation of Vizamyl images has not been evaluated and may lead to errors. Extensive brain atrophy may limit the ability to distinguish grey and white matter on a Vizamyl scan [see Dosage and Administration (2.5)]. Motion artifacts may distort the image [see Dosage and Administration (2.3)].

Vizamyl scan results are indicative of the brain neuritic amyloid plaque content only at the time of image acquisition and a negative scan result does not preclude the development of brain amyloid in the future.

Radiation Risk

Vizamyl, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure [see Dosage and Administration (2.1)].

9. Advisory Committee Meeting

No Advisory Committee meeting to discuss approval considerations for NDA 203137 was necessary.

10. Pediatrics

This application was granted a full waiver for PREA-related studies by the Pediatric Review Committee on the basis that the applicable disease / condition does not exist in children.

11. Other Relevant Regulatory Issues

The reviewer from the Office of Scientific Investigations Dr. Jong Lee reported the results of the clinical inspections. Dr Lee determined that the clinical study data were reliable. Minor deficiencies were noted. These deficiencies did not affect the studies' conclusions.

12. Labeling

Reference is made to the initial labeling provided by the Applicant and the revised versions developed by the NDA review team for an overview of the labeling negotiations. There are no outstanding labeling issues

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The reviewer for each discipline on the review team recommends approval for NDA 203137. I concur with these recommendations. Discussions regarding the product labeling have been satisfactorily completed and there are no inspectional issues that preclude approval of the application.

- Risk Benefit Assessment

Vizamyl has an acceptable risk benefit profile.

The agreed-upon labeling describes the following clinical use. Vizamyl is 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 Vizamyl scan is useful because a negative 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.

The labeling also highlights the limitations of use of Vizamyl by making it clear that a positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder and that the prognostic or predictive value of Vizamyl have not been established.

As for the risks of Vizamyl, the drug is contraindicated in patients with a history of hypersensitivity reaction to flutemetamol or any other ingredient in Vizamyl and the risks of hypersensitivity reactions are cited in the Warnings and Precautions section of the labeling. Vizamyl, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Finally the potential for errors in the interpretation of Vizamyl PET images to estimate brain neuritic plaque density is mentioned in the Clinical Studies and Dosage and administration sections of the labelling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None are necessary

- Recommendation for other Postmarketing Requirements and Commitments

None are necessary

- Recommended Comments to Applicant

There are no deficiencies that need to be communicated to the Applicant

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/s/

BRENDA Q YE
09/16/2013