

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203137Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

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<b>NDA</b>	203-137
<b>Type/Category</b>	Original-1 (Type 1- New Molecular Entity) / 1S
<b>Brand name</b>	VIZAMYL
<b>Generic name</b>	Flutemetamol F 18 Injection
<b>Proposed indication</b>	VIZAMYL (Flutemetamol F 18 Injection) is a radioactive diagnostic agent indicated with positron emission tomography (PET) imaging  (b) (4)
<b>Formulation</b>	10 mL and 30 mL multi-dose vials containing 150 MBq/mL of [18F]flutemetamol (at reference date and time for intravenous administration)
<b>Route of Administration</b>	Intravenous
<b>Applicant</b>	GE Healthcare, Inc.
<b>Reviewing Division</b>	Division of Clinical Pharmacology 5 (DCP 5)
<b>Medical Division</b>	Division of Medical Imaging Products (DMIP)
<b>Submission Dates</b>	October 26, 2012, SDN 1

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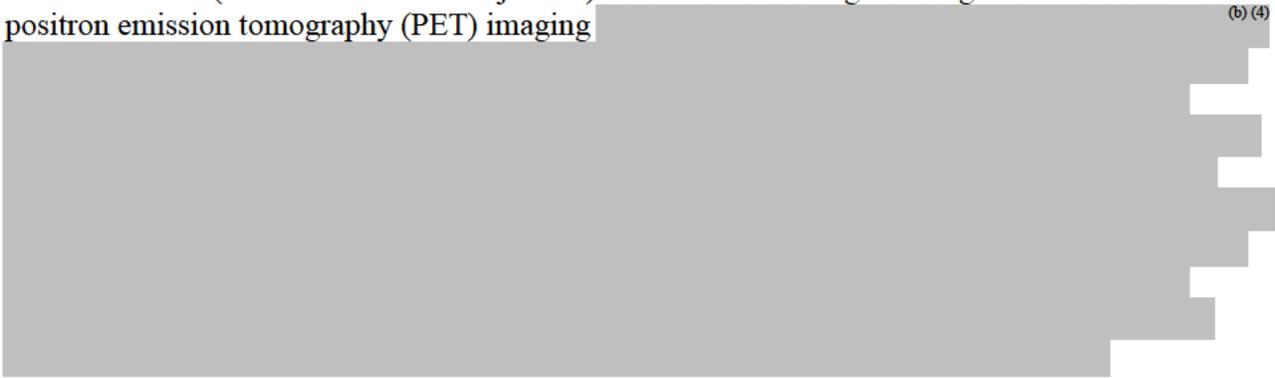
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## 1. Executive Summary

The applicant has submitted NDA for Flutemetamol F 18 Injection (Vizamyl), a new molecular entity for imaging beta amyloid in brain. The proposed indications for Flutemetamol F 18 Injection is: "VIZAMYL (Flutemetamol F 18 Injection) is a radioactive diagnostic agent indicated with positron emission tomography (PET) imaging" (b) (4)



The pivotal trial, GE067-07, was performed in end-of-life patients with probable AD. Post mortem brain biopsy was the Standard of Truth (SoT). The sensitivity of the blinded visual interpretations of PET images without anatomic images ranged from 81% to 93%. The pre-defined criterion for success, a lower bound of the 2- sided 95% exact confidence interval (CI) limit for sensitivity of >70% for at least 3 of the 5 readers, was met. The specificity of blinded visual interpretations for detecting brain fibrillar amyloid  $\beta$  without anatomic images was 44-92%. The specificity with anatomic images was 56-92%.

The proposed dose is an intravenous injection of 185 MBq or 5 mCi. The selection of dose was based on the dose escalation portion of Study ALZ103 using dosimetry (radiation exposure) and brain kinetics as dose determining factors. The effective dose (*E*) with 185 MBq is 5.9 millisieverts (mSv). The "cold" mass dose associated with this radioactive dose is 10-20  $\mu$ g.

The applicant did not conduct formal drug-drug interaction studies. However, in Study GE067-007 some patients continued taking commonly prescribed Alzheimer's disease drugs such as donepezil, memantine, galantamine et al. The composite Standard Uptake Values (SUV<sub>R</sub>) were compared for patients (n=10) taking AD medications with patients (n=58) not taking AD drugs. No significant changes were observed.

### 1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed NDA 203-137. The application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached in labeling.

## 1.2. Phase 4 Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments.

## 1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The clinical development program collected data in 761 subjects enrolled in 10 clinical studies, including two Phase 1 studies, one Phase 2 study, and seven Phase 3 studies.

Dose selection was based on the dose escalation portion of Study ALZ103. The applicant started out with 100 MBq (2.7 mCi) to two healthy volunteers and dosimetry was determined and radiation absorbed doses were estimated using OLINDA. The dose of 100 MBq resulted in 3.2 mSv of absorbed radiation dose, a value more than an order of magnitude lower than acceptable radiation dosimetry limits. The next cohort of healthy volunteers (n=4) were administered 150 MBq (4.0 mCi) of Flutemetamol F 18. Dosimetry was performed and brain kinetics of Flutemetamol F 18 were determined. The next cohort healthy volunteers (n=3) and probable Alzheimer Disease patients (n=3) were administered 185 MBq or 5.0 mCi of Flutemetamol F 18. Brain imaging was performed from 0-90 min, 150-200 min and 260-300 min post-injection. The recommended imaging time from this cohort was determined to be 80-140 min post-injection. Another cohort of healthy volunteers (n=5) and probable AD (n=5) were administered 5 mCi of tracer to acquire additional imaging time data. The optimal imaging time carried forward was 90-120 min. A clinical dose of 185 MBq (5 mCi) was chosen based on sufficient radioactivity in brain and target to non-target ratio in brain. The mass dose was < 20 microgram.

With respect to radiation exposure, the 185 MBq dose results in an effective dose (*E*) of 5.9 millisieverts (mSv). For comparison, the mean natural-source background radiation in the USA is approximately 3.1 mSv per year, and the occupational exposure limit is 50 mSv per year.

Exposure-response relationships for safety were not conducted; Phase 3 clinical trials used a single dose of 185 MBq and pharmacokinetics data were not collected.

Following intravenous injection of 185 MBq (5 mCi) of Vizamyil to humans, flutemetamol F 18 plasma concentrations declined by 75% in the first 20 minutes post-injection, and by 90% in the first 180 minutes. The F 18 in circulation during the 30-120 minutes imaging window in plasma was principally associated with flutemetamol metabolites. Excretion of <sup>18</sup>F was approximately 37% renal (28-45%; n=6) and 52% hepatobiliary (40-65%; n=6).

The applicant did not conduct formal drug-drug interaction studies. However, in Study GE067-007 some patients continued taking commonly prescribed Alzheimer's disease drugs such as donepezil, memantine, galantamine et al. The composite Standard Uptake Values (SUVR) were compared for patients (n=10) taking AD medications with patients (n=58) not taking AD drugs. No significant changes were observed.

Trials in subjects with renal or hepatic impairment were not conducted.

## 2. Question Based Review

### 2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

The clinical pharmacology information included in the NDA is limited to dosimetry and biodistribution.

**FDA Table 1.** Clinical Pharmacology Studies

Protocol	Title	Design	Population	Subjects	Primary endpoints	Secondary endpoints
ALZ103	A Phase I, Open-label Study to Assess Safety, Biodistribution, and Radiation Dosimetry and to Optimize the Imaging Protocol of AH110690 ( <sup>18</sup> F) Injection in Healthy Volunteers and Subjects with Probable Alzheimer's Disease	Open-label	HV pAD	Enrolled and analyzed: 22 (14 HV and 8 pAD)	Occurrence of AEs Physical examination abnormalities Clinical laboratory abnormalities (serum biochemistry, hematology, and urinalysis) ECG abnormalities: Vital signs (BP, heart rate, body temperature, respiratory rate, and oxygen saturation)	[ <sup>18</sup> F]Flutemetamol brain UR and DVR measured by volume-of-interest (VOI) in reference to control tissue in pAD compared to HV. Dosimetry estimates and cumulated activity by source and by entire body in HV.
GE067-014	A Phase I, Open-Label, Study to Assess a) Safety of Flutemetamol ( <sup>18</sup> F) Injection, Biodistribution and Internal Radiation Dosimetry and b) to Optimize the Imaging protocol of Flutemetamol ( <sup>18</sup> F) Injection in Japanese Healthy Volunteers and Alzheimer's Disease Subjects	Open-label	Japanese HV Japanese pAD	Enrolled and analyzed: 22 (14 HV and 8 pAD)	Occurrence of AEs Physical examination abnormalities Clinical laboratory abnormalities (serum biochemistry, hematology, and urinalysis) ECG abnormalities: Vital signs (BP, heart rate, body temperature, respiratory rate, and oxygen saturation)	[ <sup>18</sup> F]Flutemetamol brain SUVR measured by VOI analysis in pAD compared to HVs. Dosimetry estimates and cumulated activity by region and by entire body in HVs.

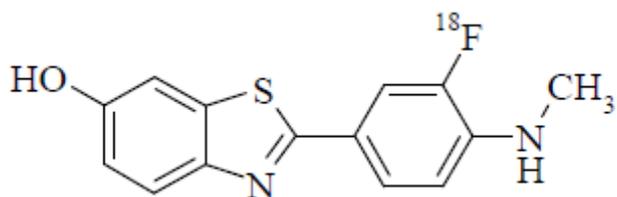
HV = healthy volunteers; pAD = probable Alzheimer's disease; N/A = not applicable; ROI = region of interest; PET = positron emission tomography; [<sup>18</sup>F]AH110690 = [<sup>18</sup>F]flutemetamol; UR = uptake ratio; DVR = distribution volume ratio; VOI = volume of interest

## 2.2. General Attributes of the Drug

### 2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Flutemetamol is a small, lipophilic, neutral molecule (**Figure 1.**) with a molecular weight of 274.32 (flutemetamol, non-radiolabelled).

Flutemetamol F 18 Injection is comprised of [<sup>18</sup>F]flutemetamol (150 MBq/mL at reference date and time), ethanol (7% v/v), sodium chloride (0.9% w/v), polysorbate 80 (0.5% w/v), phosphate buffer (0.014 M), and has a pH range of 6.0 to 8.5. The maximum total human dose (radioactive + non-radioactive) is 20 ug.



**FDA Figure 1.** Chemical structure of [<sup>18</sup>F]flutemetamol

### 2.2.2. What are the proposed mechanism of action and therapeutic indications?

The following (indented) is reproduced from the applicant's proposed package insert.

The active component of Vizamyil, flutemetamol, binds reversibly with high affinity ( $K_d = 6.7$  nM) to synthetic fibrillar  $\beta$  amyloid in human Alzheimer's brain homogenates. Specificity was demonstrated by an inhibition of binding of a known amyloid beta ligand (2-(4'-dimethylaminophenyl)-6-[<sup>125</sup>I]iodobenzothiazole, TZDM) in human brain homogenates by flutemetamol. Autoradiographic and histological studies have localized the binding of radio- or cyano-labelled flutemetamol to the AD-affected brain regions and co-localized binding to  $\beta$ -amyloid deposition. Good correlations have also been observed between the flutemetamol binding and  $\beta$ -amyloid concentration (determined by enzyme-linked immunosorbent assay; ELISA) and *in vivo* retention of [<sup>11</sup>C]PiB. [<sup>18</sup>F] flutemetamol undergoes radioactive decay releasing a positron which then interacts with an electron resulting in the release of two 511-keV gamma rays suitable for amyloid imaging. An abnormal Vizamyil scan was always accompanied by the presence of underlying fibrillar amyloid pathology. In 90% of the autopsy cohort, this agreed with dichotomy of the neuritic plaque load determined by a threshold generally considered the boundary between sparse and moderate and consistent with routine neuropathology guidelines. In 4 cases Vizamyil positivity was observed in subjects that were close to this threshold for neuritic plaques and/or had significant fibrillar amyloid deposits in diffuse plaques and/or vascular amyloidopathy indicating that significant fibrillar amyloid  $\beta$  deposits other than neuritic plaques may contribute to the Vizamyil signal.

### 2.2.3. What are the proposed dosages and routes of administration?

The recommended dose is 185 MBq (5 mCi), administered intravenously in a maximum volume of 10 mL. The total amount of flutemetamol at the 185 MBq dose is 20 ug or less.

### 2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

The first beta amyloid imaging agent, (Amyvid™; F-18 Florbetapir Injection), was approved in 2012. The following (indented) is reproduced from the Amyvid package insert.

Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate  $\beta$ -amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A

negative Amyvid 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 Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid 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. Amyvid is an adjunct to other diagnostic evaluations.

Limitations of Use:

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies.

### **2.3. General Clinical Pharmacology**

#### **2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

The NDA presents data from 8 Phase 3 studies (3 pivotal, 5 supportive), 1 Phase 2 study, and 2 Phase 1 studies. All studies except study [GE067-021] (the electronic reader training study that enrolled no subjects) assessed safety as one of the objectives.

The two Phase 1 studies ([ALZ103] and [GE067-014]) determined the biodistribution and dosimetry of [<sup>18</sup>F]flutemetamol in healthy volunteers (HV) and patients with probable Alzheimer's disease (pAD). Study ALZ103 enrolled Caucasian subjects and Study GE067-014 enrolled Asian (Japanese) subjects.

The Phase 2 study [ALZ201] provided data on the ability of [<sup>18</sup>F]flutemetamol images to differentiate between HV and subjects with AD, and the proportions of amnesic mild cognitive impairment (aMCI) subjects with normal and abnormal [<sup>18</sup>F]flutemetamol images.

Seven of the eight Phase 3 studies determined the validity (sensitivity and/or specificity, PPV, and NPV) and reproducibility (IRA and IRR) of the blinded visual assessment of [<sup>18</sup>F]flutemetamol PET images. In all but one study (the electronic reader training study, GE067-021), image readers were trained in person by a consultant nuclear medicine physician who used material provided by GE Healthcare; in the electronic reader training study (Study GE067-021), readers were training using an electronic training program, also provided by GE Healthcare.

The eighth Phase 3 study, [GE067-005], is an on-going study assessing the ability of [<sup>18</sup>F]flutemetamol images to predict the subsequent development of AD in aMCI subjects.

**FDA Table 2.** Table of Clinical Studies

Phase	Study	Brief Description	Location	Dosing/Product	Target Activity	Subjects					Total
						EOL <sup>a</sup>	pAD	aMCI	NPH	HV	
1	ALZ103	Safety, BD, dosimetry	Europe	Single/Flutemetamol <sup>b</sup>	100, 150, or 185 MBq		8			14	22
	GE067-014	Safety, BD, dosimetry in Japanese	Japan	Single/Flutemetamol <sup>b</sup>			8			14	22
2	ALZ201	Phase 2 proof-of-concept	8 centres in Europe	Single/Flutemetamol <sup>b</sup> , OR Double/Flutemetamol <sup>b</sup> , OR Separate single/Flutemetamol <sup>b</sup> AND single [ <sup>11</sup> C]PiB	185 MBq 120 MBq 333 MBq <sup>11</sup> C-PiB		27	20		25	72
3	GE067-005	Prediction of aMCI-to-AD conversion	28 centres in US and Europe	Single/Flutemetamol <sup>b</sup>	185 MBq				232		232
	GE067-007	Brain autopsy study	19 centres in US and UK	Single/Flutemetamol <sup>b</sup>	185-370 MBq	180					180
	GE067-008	Brain biopsy study	1 centre in US	Single/Flutemetamol <sup>b</sup>	185 MBq				7		7
	GE067-009	Brain biopsy study	1 centre in US	Single/Flutemetamol <sup>b</sup>	185 MBq				12		12
	GE067-010	Brain biopsy study	1 centre in Finland	Single/Flutemetamol <sup>b</sup>	185 MBq				15		15
	GE067-011	Brain biopsy study	4 centres in Finland	Single/Flutemetamol <sup>b</sup>	185 MBq				18		18
	GE067-015	HV specificity study	10 centres in US and Europe	Single/Flutemetamol <sup>b</sup>	185 MBq					181	181
	GE067-021 <sup>c</sup>	Electronic reader training study <sup>c</sup>	US	Not applicable	Not applicable						
	Total					180	43	252	52	234	761

BD = biodistribution; EOL = end of life; HV = healthy volunteer; MBq = megabecquerels; aMCI = amnesic mild cognitive impairment; PiB = Pittsburgh Compound B; NPH = normal pressure hydrocephalus; pAD = probable Alzheimer's disease; UK = United Kingdom; US = United States.

<sup>a</sup> Life expectancy <1 year and ≥55 years of age.

<sup>b</sup> Flutemetamol F 18 Injection.

<sup>c</sup> No subjects were enrolled in this study, which used images collected in the other studies.

REF: CSRs for [ALZ103], [ALZ201], [GE067-005], [GE067-007], [GE067-008], [GE067-009], [GE067-010], [GE067-011], [GE-67-014], [GE067-015], and [GE067-021].

The pivotal trial, GE-07, was performed in end-of-life patients with probable AD. Post mortem brain biopsy was the Standard of Truth (SoT). The sensitivity of the blinded visual interpretations of PET images without anatomic images ranged from 81% to 93%. The pre-defined criterion for success, a lower bound of the 2- sided 95% exact confidence interval (CI) limit for sensitivity of >70% for at least 3 of the 5 readers, was met. The specificity of blinded visual interpretations for detecting brain fibrillar amyloid β without anatomic images was 44-92%. The specificity with anatomic images was 56-92%.

### 2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

### 2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moieties in plasma and clinically relevant tissues were not identified and measured to assess pharmacokinetic parameters and no exposure-response relationship was studied. Only one dose was used for clinical studies.

## 2.4. Exposure-Response

### 2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?

### 2.4.2. What are the characteristics of the exposure-response relationships for safety?

Dose selection was based on the dose escalation portion of Study ALZ103. The applicant started out with 100 MBq (2.7 mCi) to two healthy volunteers and dosimetry was determined and radiation absorbed doses were estimated using OLINDA. The dosimetry was reviewed and the next cohort of healthy volunteers (n=4) were administered, 150 MBq (4.0 mCi) of Flutemetamol F 18. The dosimetry was performed and brain kinetics of Flutemetamol F 18 were determined. The next cohort healthy volunteers (n=3) and probable Alzheimer Disease patients (n=3) were administered 185 MBq or 5.0 mCi of Flutemetamol F 18. Brain imaging was performed from 0-90 min, 150-200 min and 260-300 min post-injection. The recommended imaging time from this cohort was determined to be 80-140 min post-injection. Another cohort of healthy volunteers (n=5) and probable AD (n=5) were administered 5 mCi of tracer to acquire additional imaging time data. The optimal imaging time for Phase 2 clinical studies was further optimized to be 90-120 min. A clinical dose of 185 MBq (5 mCi) was chosen based on sufficient radioactivity in brain and target to non-target ratio in brain. The mass dose was < 20 microgram.

With respect to radiation exposure, the 185 MBq dose results in an effective dose (*E*) of 5.9 millisieverts (mSv). For comparison, the mean natural-source background radiation in the USA is approximately 3.1 mSv per year, and the occupational exposure limit is 50 mSv per year.

Exposure-response relationships for safety were not conducted; Phase 3 clinical trials used a single dose of 185 MBq and pharmacokinetics data were not collected.

#### **2.4.3. Does this drug prolong QT/QTc Interval?**

743 subjects contributed QTc-Fridericia data. Ninety-two percent of subjects had categorical changes of ≤30 ms and the percentages of subjects with changes of >30 ms to 45 ms, >45 ms to 60 ms, and >60 ms change were similar with respect to increases and decreases. The shift table showed a post-dosing 3.6% increase in the number of High values at the expense of Normal values. The mean change from baseline was 3.6 ms (0.9%).

The mass amount of flutemetamol is 20 microgram or less. A clinically significant effect of [<sup>18</sup>F]Flutemetamol on QT/QTc prolongation is not expected.

#### **2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Based upon the route to dose selection (see 2.4.1.), the selected dose is likely as low as reasonably achievable (ALARA). No additional exposure-response relationship was determined for this single administration drug given as a microdose.

### **2.5. Pharmacokinetics**

#### **2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

#### **2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

A biodistribution study was conducted in European and Japanese subjects and patients using a single dose of flutemetamol. Multiple dose PK was not conducted as flutemetamol will be administered only once as a diagnostic adjunct. Following intravenous injection of 185 MBq (5 mCi) of Vizamyl to humans, flutemetamol F 18 plasma concentrations declined by 75% in the first

20 minutes post-injection, and by 90% in the first 180 minutes. The F 18 in circulation during the 30-120 minutes imaging window in plasma was principally associated with flutemetamol metabolites.

**2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

The applicant does not report inter-subject variability in circulating drug, and has not studied intra-subject variability in circulating drug. However, the applicant did study intra-individual variability in selected brain regions in healthy volunteers and probable AD patients in Study GE-201.

[<sup>18</sup>F]flutemetamol was administered to the same individuals after a two week washout period. Test-retest Standard Uptake Value Ratio had a low inter-subject variability.

**FDA Table 3.** Mean Test-retest Variability [(Test ÷ Retest)/Test\*100%] in Standard Uptake Value Ratio (SUVR) for 5 pAD Subjects

Brain VOI	Mean test-retest Variability, 5 ADs (%)
Anterior cingular cortex	2.0 ± 0.9
Frontal cortex	1.4 ± 0.4
Lateral temporal cortex	1.8 ± 0.8
Medial temporal cortex	3.8 ± 2.4
Occipital cortex	0.9 ± 0.5
Parietal cortex	2.1 ± 1.8
Pons	3.1 ± 2.7
Posterior cingular cortex	1.2 ± 0.5
Sensorimotor cortex	2.2 ± 1.8
Striatum	0.9 ± 0.5
Subcortical white matter	3.2 ± 2.1
Mean	2.1 ± 1.0

VOI = Volume of interest; pAD = probable Alzheimer’s disease; PET = Positron emission tomography.

**2.5.4. What are the characteristics of drug absorption?**

[<sup>18</sup>F]flutemetamol is administered as a single-time intravenous injection. It is 100% bioavailable to the systemic circulation.

**2.5.5. What are the characteristics of drug distribution?**

The pattern of distribution of radioactivity appears below (**Table 4**).

**FDA Table 4.** Estimated Radiation Absorbed Doses (from proposed package insert)

Target Organ/Tissue	Absorbed Radiation Dose $\mu\text{Gy}/\text{MBq}$
Adrenals	13
Brain	11
Breasts	5
Gallbladder wall	287
Heart wall	14
Kidneys	31
Liver	57
Lower large intestine wall	42
Lungs	16
Muscle	9
Osteogenic cells	11
Ovaries	25
Pancreas	15
Red marrow	13
Skin	5
Small intestine wall	102
Spleen	15
Stomach wall	12
Testes	8
Thymus	6
Thyroid	6
Upper large intestine wall	117
Urinary bladder wall	145
Uterus	25
Total body	12
<b>Effective Dose</b>	<b>32<math>\mu\text{Sv}/\text{MBq}</math></b>

The calculated mean effective dose was 32 $\mu\text{Sv}/\text{MBq}$ , resulting in an effective dose ( $E$ ) of 5.9 millisieverts (mSv) when 185 MBq is administered.

**2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Mass balance study results are not reported. However, based on imaging, excretion of  $^{18}\text{F}$  was approximately 37% renal (28-45%; n=6) and 52% hepatobiliary (40-65%; n=6).

**2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**

**2.5.8. What are the characteristics of drug metabolism?**

Following intravenous injection of the recommended dose of 185 MBq of VIZAMYL to humans, [18F]flutemetamol plasma concentrations declined by 75% in the first 20 min post-injection and by 90% in the first 180 minutes. The  $^{18}\text{F}$  in circulation during the 30-120 minutes imaging window in plasma was principally associated with flutemetamol metabolites, but the identity of metabolites was not determined.

**2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?**

There is not direct evidence for excretion of parent drug and/or metabolites into bile, but based on <sup>18</sup>F imaging, biliary excretion appears to be present (see 2.5.6).

**2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?**

There is not evidence for enterohepatic recirculation for parent and/or metabolites, but only limited concentration-time data are reported, and data following non-IV administration are not reported.

**2.5.11. What are the characteristics of drug excretion in urine?**

Based on imaging, elimination of <sup>18</sup>F was approximately 37% renal (28-45%; n=6).

**2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Dose proportionality results are not reported.

**2.5.13. How do the PK parameters change with time following chronic dosing?**

Flutemetamol F 18 Injection is administered only one time for diagnostic imaging. Repeat dosing results are not reported.

**2.5.14. Is there evidence for a circadian rhythm of the PK?**

There is not evidence for a circadian rhythm of the PK, but only limited concentration-time data are reported, and data are not reported by time-of-day.

**2.6. Intrinsic Factors**

**2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

The inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) is not reported.

**2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?**

**2.6.2.1. Severity of Disease State**

**2.6.2.2. Body Weight**

**2.6.2.3. Elderly**

No PK data is reported on severity of disease state or body weight or age.

#### **2.6.2.4. Pediatric Patients**

Data from pediatric patients are not reported. A pediatric waiver has been granted to the applicant.

#### **2.6.2.5. Race/Ethnicity**

The effect of race/ethnicity on imaging or PK are not reported.

#### **2.6.2.6. Renal Impairment**

The effect of renal impairment on imaging or PK are not reported.

#### **2.6.2.7. Hepatic Impairment**

The effect of hepatic impairment on imaging or PK are not reported.

#### **2.6.2.8. What pregnancy and lactation use information is available?**

No pregnancy or lactation use information is available.

#### **2.6.3. Does genetic variation impact exposure and/or response?**

The effect of genetic variation impact on exposure and/or response is not reported.

### **2.7. Extrinsic Factors**

#### **2.7.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

#### **2.7.2. Is the drug a substrate of CYP enzymes?**

#### **2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?**

#### **2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**

*In vitro* investigation of drug metabolism is not reported.

#### **2.7.5. Are there other metabolic/transporter pathways that may be important?**

No atypical pathways have been reported.

#### **2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**

The effect of extrinsic factors influence on exposure and/or response is not reported.

#### **2.7.7. What are the drug-drug interactions?**

The applicant did not conduct formal drug-interaction studies. However, in Study GE067-007, some patients continued taking commonly prescribed Alzheimer's Disease drugs such as donepezil,

memantine, galantamine, et al. The composite SUVR scores for cortical regions were compared for patients (n=10) taking AD medications with patients (n=58) not taking AD drugs.

**FDA Table 5.** Composite SUVR (Cerebellar Cortex) by Select Concomitant Medication Use (*Post-mortem* Analysis Set, N = 68)

Select Concomitant Medication Use <sup>a</sup> , Statistic	Composite SUVR
Yes, n	10
Mean (Standard Deviation)	2.1509 (0.42852)
Median	2.329
Minimum, Maximum	1.343, 2.825
95% Confidence Interval	1.844, 2.457
No, n	58
Mean (Standard Deviation)	1.8657 (0.52238)
Median	1.842
Minimum, Maximum	1.014, 3.137
95% Confidence Interval	1.728, 2.003

a Subjects were classified based on the following concomitant medication usage: RIVASTIGMINE, DONEPEZIL, MEMANTINE, GALANTAMINE. These are medications commonly prescribed to patients with Alzheimer’s disease.

b Composite SUVR is defined as an average of frontal, anterior cingulate gyri, parietal, lateral-temporal and posterior cingulate gyri /precuneus uptake following administration of Flutemetamol F 18 Injection

Use of AD medication is not associated with a significant difference in SUVR.

**2.7.8. Does the label specify co-administration of another drug?**

The package insert does not specify co-administration of another drug.

**2.7.9. What other co-medications are likely to be administered to the target population?**

See section 2.7.7.

**2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

No mechanistic basis for pharmacodynamic (PD) drug-drug interactions is reported. Due to the low dose, (approximately 10-20 ug), flutemetamol is unlikely to cause non-imaging PD effects or contribute to PD drug interactions.

**2.8 General Biopharmaceutics**

**2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

**2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?**

**2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

**2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**

**2.8.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

**2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?**

**2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

Flutemetamol F 18 is an intravenously administered simple aqueous solution, the above biopharmaceutics questions are not applicable.

## **2.9. Analytical Section**

**2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?**

**2.9.2. Which metabolites have been selected for analysis and why?**

**2.9.3. For all moieties measured, is free, bound, or total measured?**

**2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?**

**2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?**

**2.9.5.1. What are the lower and upper limits of quantitation?**

**2.9.5.2. What are the accuracy, precision, and selectivity at these limits?**

**2.9.5.3. What is the sample stability under conditions used in the study?**

**2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?**

The analytical method used for the PK data reported in the NDA was HPLC with radiochemical detection. Analytical methods data was not submitted in the NDA, nor was it submitted in response to an FDA information request made during the review cycle. In response to the information request, the applicant did indicate that non-radiolabelled moieties were not followed. Because pharmacokinetics data is of limited impact to prescribing and dosing, the reviewer accepted the inability to verify the performance of analytical methods.

## **3. Detailed Labeling Recommendations**

The reviewer's recommendations for changes to sections **7 DRUG INTERACTIONS** and **12 CLINICAL PHARMACOLOGY** of GE Healthcare's proposed package insert appear on the next page as "track changes."

## 7. DRUG INTERACTIONS

(b) (4) ~~Pharmacodynamic~~ drug-drug interaction studies have not been performed in subjects to establish the extent, if any, to which concomitant medications may alter VIZAMYL image results.

(b) (4) ~~W~~within a clinical study of subjects with a range of cognitive impairment, some (b) (4) were receiving the following medications: donepezil, galantamine, memantine, (b) (4) rivastigmine. Mean cortical Standardized Uptake Value (SUV) ratios did not differ between the (b) (4) taking or not taking these concomitant medications. (b) (4)

## 12. CLINICAL PHARMACOLOGY

### 12.1. Mechanism of Action

Flutemetamol F 18 binds to  $\beta$ -amyloid plaques (b) (4) the F 18 isotope produces a positron signal that is detected by a PET scanner. In *in vitro* binding studies using postmortem human brain homogenates containing fibrillar  $\beta$ -amyloid the dissociation constant (b) (4)

(b) (4) for flutemetamol was 6.7 (b) (4) Kd (b) (4)

Selectivity of [ $^3$ H]flutemetamol binding in post-mortem human brain sections was demonstrated using autoradiography, silver-stained protein, and immunohistochemistry (monoclonal antibody to  $\beta$ -amyloid) correlation studies. (b) (4)

## 12.2. Pharmacodynamics

(b) (4)

Following intravenous injection, flutemetamol F 18 diffuses across the human blood brain barrier and produces a radioactivity signal detectable throughout the brain. Subsequently, cerebral perfusion decreases the brain flutemetamol F 18 content, with differential retention of the drug in areas that contain  $\beta$ -amyloid aggregates compared to areas that lack the aggregates. The time-activity curves for flutemetamol F 18 in the brain of subjects with positive scans show continual signal increases from time zero through 30 minutes post administration, with stable values thereafter up to at least 120 minutes post injection. Differences in the signal intensity between (b) (4) brain that specifically retain flutemetamol F 18 and (b) (4) brain with nonspecific retention of the drug form the basis of image interpretation methods [see Dosage and Administration (2.4)].

The test-retest distribution of flutemetamol F 18 was evaluated in 5 subjects with probable AD who underwent two administrations -of flutemetamol F 18 (followed by PET scans) separated by a time period of 1 to 4 weeks. Images were reproducible when evaluated semi quantitatively using an automated assessment of SUV in pre-specified cortical regions of brain.

## 12.3. Pharmacokinetics

Following intravenous injection of (b) (4) 185 MBq of VIZAMYL in (b) (4) humans, (b) (4) flutemetamol F 18 plasma concentrations declined by 75% in the first (b) (4) -20 minutes post-injection and by 90% (b) (4) in the first 180 minutes. (b) (4)

The F 18 in circulation during the 30-120 minutes imaging window in plasma was principally associated with flutemetamol metabolites.

(b) (4) Excretion was approximately 37% renal (28-45%; n=6) and 52% hepatobiliary (40-65%; n=6).

## **Appendices**

**4.1. Applicant's Proposed Package Insert (original, annotated)**

**4.2. Cover sheet and OCPB Filing/Review Form**

APPEARS THIS WAY ON ORIGINAL

**4.1. Applicant's Proposed Package Insert (original, annotated)**

APPEARS THIS WAY ON ORIGINAL

**1.14.1.2 Annotated labeling text**

The annotated draft labeling text is provided on the following pages in a tabular format. The left column contains the proposed text per section, the middle column contains the section(s) within the application that support the proposed text, and the right column contains additional information for the reviewer as appropriate. As this is an electronic submission, the sections noted in the middle column are links that will take the reviewer to the source document.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 4.2. Cover sheet and OCPB Filing/Review Form

APPEARS THIS WAY ON ORIGINAL

**CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR  
NDA/BLA or Supplement**

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<u><b>General Information About the Submission</b></u>				
	Information		Information	
NDA/BLA Number	203-137		Brand Name	Flutemetamol (18F) Injection
OCP Division (I, II, III, IV, V)	V		Generic Name	N/A
Medical Division	Division of Medical Imaging		Drug Class	Imaging
OCP Reviewer	Christy John, Ph.D.		Indication(s)	For the visual detection of $\beta$ amyloid neuritic plaques in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other cognitive complaints.
OCP Team Leader	Gene Williams, Ph.D.		Dosage Form	Solution for Injection
Pharmacometrics Reviewer	N/A		Dosing Regimen	Single dose of 5 mCi
Date of Submission	October 26, 2012		Route of Administration	Intravenous Injection
Estimated Due Date of OCP Review	April 26, 2013		Sponsor	GE Healthcare
Medical Division Due Date	May 15, 2013		Priority Classification	1S
PDUFA Due Date	October 26, 2013			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any

## CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:	X	1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				

## CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?		X		
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

## CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		X		
5	Has a rationale for dose selection been submitted?	X			No formal dose finding study was conducted by the sponsor.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The sponsor is seeking a pediatric waiver.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

## CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

     YES     

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no potential review issues for 74-day letter.

Christy S John, Ph.D.

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Reviewing Clinical Pharmacologist

Gene Williams, Ph.D.

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Team Leader/Supervisor

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/s/  
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CHRISTY S JOHN  
12/07/2012

GENE M WILLIAMS  
12/10/2012

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CHRISTY S JOHN  
06/26/2013

GENE M WILLIAMS  
06/26/2013

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