Play a part in understanding the clinical value of amyloid imaging for patients with Alzheimer's disease

Join the IDEAS Study

Imaging Dementia – Evidence for Amyloid Scanning (IDEAS)

The IDEAS Study is a clinical trial approved by the Commission for Medicare and Medicaid Services (CMS) entitled “Imaging Dementia — Evidence for Amyloid Scanning (IDEAS) Study: A Coverage with Evidence Development Longitudinal Cohort Study” sponsored by the American College of Radiology (ACR). ACR has been selected to act as the operations center for the IDEAS Study and will act as the Sponsor for the study, which will be funded by GE Healthcare and other commercial manufacturers of β-amyloid radiopharmaceutical tracers.
Be part of the IDEAS Study to help assess the value of amyloid imaging in evaluating outcomes in patients with cognitive impairment.

The purpose of the research study titled Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study is to determine the clinical usefulness of a brain positron-emission tomography (PET) scan that detects amyloid plaques, a core feature of Alzheimer’s disease.

The study’s objective is to assess whether PET amyloid imaging will promote beneficial changes in patient care through increased certainty of diagnosis and early utilization of counseling and medical interventions.

Specifically, the IDEAS Study will assess the impact of amyloid PET on:

1. The management of patients meeting Appropriate Use Criteria (AUC)
2. Major medical outcomes (such as hospital admissions and emergency room visits), over 12 months, in patients enrolled in the study, compared to matched patients not in the study
Help evaluate and promote positive patient outcomes.

Vizamyl is one of the three FDA-approved amyloid imaging tracers that will be part of the IDEAS Study. To learn more about Vizamyl, please visit GEVizamyl.com, or contact GE Healthcare Medical Affairs at 800 654 0118 (option 2, then option 3), or via email at professionalservices.medical@ge.com.

We invite you to use Vizamyl in the IDEAS Study.
# The IDEAS Study

The IDEAS Study is enrolling dementia experts and imaging centers to refer and perform PET amyloid scans on cognitively impaired patients.

## Qualifications for participation

<table>
<thead>
<tr>
<th>Dementia Specialist Qualifications</th>
<th>Imaging Site Qualifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Training</strong></td>
<td><strong>Accreditation</strong></td>
</tr>
<tr>
<td>Be trained and board-certified in neurology, psychiatry, or geriatric medicine.</td>
<td>Freestanding PET facilities must be accredited for PET imaging by the ACR, IAC, or Radsite. Hospital-based PET facilities must be accredited by a <strong>Medicare-approved hospital accrediting agency (for example, The Joint Commission)</strong>; additional accreditation by the ACR, IAC, or Radsite is optional.</td>
</tr>
<tr>
<td><strong>Experience</strong></td>
<td><strong>Experience</strong></td>
</tr>
<tr>
<td>Devote 25% or more of patient contact time to the evaluation and care of adults with acquired cognitive impairment or dementia.</td>
<td>Sites must have documented experience performing FDG brain scans or amyloid imaging using any of the three FDA-approved agents. Brain scans include: PET, PET/CT, or PET/MRI.</td>
</tr>
<tr>
<td><strong>Approval</strong></td>
<td><strong>Training — Interpreting physicians must:</strong></td>
</tr>
<tr>
<td>Obtain approval of an IRB (through ACR or a local IRB).</td>
<td>1. Be <strong>board-certified</strong> in radiology or nuclear medicine.</td>
</tr>
<tr>
<td><strong>Contract</strong></td>
<td>2. Complete reader training for the amyloid tracer they will use.</td>
</tr>
<tr>
<td>Each dementia specialist will be included in a contractual agreement with the ACR, which will ensure eligibility and facilitate payment for submitted data.</td>
<td>3. <strong>Consent</strong> to participate in, and adhere to, protocol procedures.</td>
</tr>
</tbody>
</table>

IRB, Institutional Review Board; ACR, American College of Radiology; IAC, Intersocietal Accreditation Commission; CT, computed tomography; MRI, magnetic resonance imaging; FDG, fluorodeoxyglucose; FDA, Food and Drug Administration.
## Participating in the study

<p>| | |</p>
<table>
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</table>
| 1 | Patients will be recruited  
Dementia specialists participating in the study will identify patients who meet the AUC, screen them, and obtain their consent to participate. |
| 2 | Dementia specialists will refer to PET facilities  
Dementia specialists will refer patients to participating PET facilities in their area to perform an amyloid PET scan. |
| 3 | PET facilities will scan patients within 30 days  
Results will be interpreted by a qualified physician and provided to the referring dementia specialist for support in further decision-making. |
| 4 | PET facilities will submit claims to CMS  
PET facilities will be reimbursed for global or technical and professional services and will contribute $50 for each patient imaged as part of the IDEAS Study (through an established escrow account with the ACR, with a minimum balance of $250). |

Prior to Vizamyl administration, please read the [Full Prescribing Information](#).
Enroll to become a qualified referring physician or imaging site

How to enroll:

1. Ensure that you meet all of the qualifications for participation. For additional assistance in becoming qualified, contact your local GE Healthcare Sales Specialist.

2. Complete and submit your registration form online to the ACR. To register, click on Login/Register at www.ideas-study.org.

3. The ACR will have final approval on the acceptance of qualified dementia experts and PET facilities into the study.

Contact your local GE Healthcare Sales Specialist for more information on enrolling in the IDEAS Study.

ACR, American College of Radiology.

From harnessing the power of nuclear medicine to finding a smarter path to personalized care with PET radioisotopes, GE Healthcare is committed to working with you to provide products, services, and solutions that address your molecular imaging needs.

Prior to Vizamyl administration, please read the Full Prescribing Information.
**INDICATIONS AND USAGE**

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 (1).

**Limitations of Use:**
- A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder (1)
- Safety and effectiveness of Vizamyl have not been established for:
  - Predicting development of dementia or other neurological condition (1)
  - Monitoring responses to therapies (1)

**DOSAGE AND ADMINISTRATION**

- Use appropriate radiation safety handling measures (2.1)
- Administer 185 megabecquerels (MBq) (5 millicuries (mCi)) within 40 seconds as a single intravenous bolus in a total volume of 10 mL or less (2.2)
- Follow injection with an intravenous flush of 5 to 15 mL of 0.9% sterile sodium chloride injection (2.2)
- Obtain 20-minute PET images starting approximately 90 minutes after intravenous injection (2.3)
- Image interpretation: Refer to full prescribing information (2.4, 2.5)
- The radiation dose absorbed from a 185-MBq (5-mCi) dose of Vizamyl is 5.92 mSv in an adult (2.6)

**CONTRAINDICATIONS**

- Known hypersensitivity to Vizamyl or any excipient, including polysorbate 80 (4).

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity reactions: Ask patients about prior reactions to Vizamyl. Observe for hypersensitivity signs and symptoms following Vizamyl administration. Have resuscitation equipment and trained personnel available at time of Vizamyl administration (5.1)
- Image interpretation errors (especially false positives) have been observed (5.2)
- Radiation risk: Vizamyl, similar to all radiopharmaceuticals, contributes to a patient’s long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure (2.1, 5.3)

**ADVERSE REACTIONS**

Most commonly reported adverse reactions were flushing (2%), headache (1%), increased blood pressure (2%), nausea (1%), and dizziness (1%).

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2014
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
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) and 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 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 in 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:
  - Predicting development of dementia or other neurologic condition.
  - Monitoring responses to therapies.

2 DOSAGE AND ADMINISTRATION
2.1 Radiation Safety - Drug Handling
Vizamyl is a radioactive drug and should be handled with safety measures to minimize radiation exposure during administration (see Warnings and Precautions (5.3)). Use waterproof gloves and effective shielding, including lead-glass syringe shields when handling and administering Vizamyl. To minimize radiation dose to the bladder, encourage patients to urinate before and after Vizamyl administration in order to permit frequent voiding. Encourage patients to void before and after imaging with Vizamyl and frequently thereafter for 24 hours following Vizamyl administration.

2.2 Recommended Dosing and Administration Procedures
The recommended dose for Vizamyl is 185 megabecquerels (MBq) (5 milliCi) in a maximum dose volume of 10 mL, administered as a single intravenous bolus within 40 seconds. The maximum mass dose is 20 micrograms. Follow the injection with an intravenous flush of 5 to 15 mL of 0.9% sterile sodium chloride injection.
- Use aseptic technique and radiation shielding to withdraw and administer Vizamyl solution.
- Calculate the necessary volume to administer based on calibration time and dose using a suitably calibrated instrument.
- Visually inspect Vizamyl for particulate matter and discoloration prior to administration. Do not administer Vizamyl if it contains particulate matter or is discolored (see Description (1.1)).
- Do not dilute Vizamyl.
- Dispose of unused product in a safe manner in compliance with applicable regulations (see How Supplied/Storage and Handling (16)).

2.3 Imaging Acquisition Guidelines
A 20-minute PET image should be acquired starting 90 minutes after Vizamyl injection, using a PET scanner in 3-D mode with appropriate data corrections. Position the patient supine with the brain (including the cerebellum) within a single field of view. The patient’s head should be tilted so that the anterior commissure-posterior commissure (AC-PC) plane is at right angles to the bore-axis of the PET scanner, with the head positioned in a suitable head support. Reducing head movement with tape or other flexible head restraints may be employed.

Iterative or filtered back-projection reconstruction is recommended with a slice thickness of 2 to 6 mm, matrix size of 128 x 128 with pixel sizes of approximately 2 mm. Where a post-smoothing filter is applied, a full width half maximum (FWHM) of not more than 5 mm is recommended; filter FWHM should be chosen to optimize the signal-to-noise ratio while preserving the sharpness of the reconstructed image.

2.4 Image Orientation and Display
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; the anterior and posterior aspects of the corpus callosum should be parallel to the AC-PC line as shown in Figure 2.

Image Display
- Display images with all planes (axial, sagittal and coronal planes) linked by crosshairs.
- Select a color scale that provides a progression of low through high intensity (e.g., rainbow or Sakllof). The selected color scale should (1) provide colors that allow the reader to discriminate intensity levels above and below the intensity level of the pons, (2) provide a 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 flutemetamol F 18 uptake as described in Image Interpretation below:
  - Frontal lobes (axial, with optional sagittal plane view)
  - Posterior cingulate and precuneus (axial, with optional coronal plane view)
  - Lateral temporal lobes (axial, with optional coronal plane view)
  - Inferolateral parietal lobes (coronal, with optional axial plane view)
  - Striatum (axial, with optional sagittal plane view)

2.5 Image Interpretation
Vizamyl images should be interpreted only by readers who successfully complete the electronic training program provided by the manufacturer (see Warnings and Precautions (5.2)). 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.

Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of image assessment (see Warnings and Precautions (5.2)). Images are designated as positive or negative either by comparing radioactivity in cortical grey matter with activity in adjacent white matter, or based on the intensity in the five regions mentioned above. 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). Images should be viewed with the minimum image intensity set to zero and the maximum set such that the signal level in the easily identifiable pons is at 90% of maximum.

Negative scans show more radioactivity in white matter than in grey matter, creating clear grey-white matter contrast.
Specifically, a negative scan would have the following characteristics:
- frontal, lateral temporal, inferolateral parietal: 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 or lower 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: 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,
- 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,
- 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 flutemetamol F 18 uptake (see Image Orientation and Display above) is positive in either hemisphere, then the scan is considered positive. Otherwise, the scan is considered negative.

Among patients with clinically important β-amyloid neuritic plaques in the brain, the temporal lobes, parietal lobes, and striatum may not be as affected compared to other brain regions. Therefore, in some images, flutemetamol F 18 signal in these regions may not be as intense as in the frontal lobes or the posterior cingulate and precuneus regions.

Atrophy may affect the interpretability of scans, particularly in the frontal, temporal and parietal lobes (see Warnings and Precautions (5.2)). For cases in which atrophy is apparent or suspected and there is uncertainty as to the location of the grey matter on the PET scan, examine the striatum for flutemetamol F 18 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, suboptimal patient positioning, or over-smoothing of the reconstructed image.

Figure 1: Axial view of negative (left) and positive (right) Vizamyl scans. The axial slices which cut through the frontal pole and inferior aspect of the splenium are shown using a rainbow color scale. The left image shows a white matter sulcal pattern at the frontal (f) and lateral temporal (lt) regions with a color intensity that tapers to the periphery, as well as less radioactivity in the striatal region(s). The right image shows absence of the white matter sulcal pattern with intensity radiating to a sharply defined convex edge, as well as more radioactivity in the striatum. In both the frontal and lateral temporal regions, the intensity is higher in the grey matter regions of the right image compared to those of the left image.
Figure 2: Sagittal view of negative (left) and positive (right) Vizamyl scans. The sagittal slices are slightly off midline in one hemisphere and shown using a rainbow color scale. In the posterior cingulate (pc) region, which is superior and posterior to the corpus callosum (cc), the left image shows intensity below 50% of peak intensity whereas the right image shows intensity above 60% of peak intensity. The pons (p) is set to approximately 90% of the maximum intensity.

Figure 3: Coronal view of negative (left) and positive (right) Vizamyl scans. The coronal slices are located posterior to the corpus callosum. The left image shows a white matter sulcal pattern in the inferior parietal (ip) regions that is not evident in the right image. Relative to the left image, the right image shows increased intensity in the posterior cinguli (pc) and increased radial extent of high intensity to the lateral surfaces of the parietal lobes particularly evident in the inferior parietal regions.

### 2.6 Radiation Dosimetry

The estimated absorbed radiation doses for adult patients following intravenous injection of Vizamyl are shown in Table 1. Values were calculated from human biodistribution data using OLINDA/EXM software and assuming emptying of the urinary bladder at 3.5 hour intervals.

The adult effective dose resulting from a 185-MBq (5-mCi) Vizamyl administration is 5.92 mSv. The use of a CT scan to calculate attenuation correction for reconstruction of Vizamyl images (as done in PET/CT imaging) will add radiation exposure at the level of approximately 0.1 mSv effective dose. Diagnostic head CT scans using helical scanners administer an average of 2.2 x 1.3 mSv effective dose. The actual radiation dose is operator and scanner dependent.
Table 1: Adult Estimated Radiation Absorbed Vizamyl Doses in Organs/Tissues

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Absorbed Radiation Dose Per Unit Administered Activity microGy/MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>13</td>
</tr>
<tr>
<td>Brain</td>
<td>11</td>
</tr>
<tr>
<td>Breasts</td>
<td>5</td>
</tr>
<tr>
<td>Gallbladder wall</td>
<td>287</td>
</tr>
<tr>
<td>Heart wall</td>
<td>14</td>
</tr>
<tr>
<td>Kidneys</td>
<td>31</td>
</tr>
<tr>
<td>Liver</td>
<td>57</td>
</tr>
<tr>
<td>Lower large intestine wall</td>
<td>42</td>
</tr>
<tr>
<td>Lungs</td>
<td>16</td>
</tr>
<tr>
<td>Muscle</td>
<td>9</td>
</tr>
<tr>
<td>Osteogenic cells</td>
<td>11</td>
</tr>
<tr>
<td>Ovaries</td>
<td>25</td>
</tr>
<tr>
<td>Pancreas</td>
<td>15</td>
</tr>
<tr>
<td>Red marrow</td>
<td>13</td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
</tr>
<tr>
<td>Small intestine wall</td>
<td>102</td>
</tr>
<tr>
<td>Spleen</td>
<td>15</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>12</td>
</tr>
<tr>
<td>Testes</td>
<td>8</td>
</tr>
<tr>
<td>Thymus</td>
<td>6</td>
</tr>
<tr>
<td>Thyroid</td>
<td>6</td>
</tr>
<tr>
<td>Upper large intestine wall</td>
<td>117</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>145</td>
</tr>
<tr>
<td>Uterus</td>
<td>25</td>
</tr>
<tr>
<td>Total body</td>
<td>12</td>
</tr>
<tr>
<td>Effective Dose</td>
<td>32 (microSv/MBq)</td>
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</tbody>
</table>

3  DOSAGE FORMS AND STRENGTHS
Vizamyl injection is available in a 10-mL or 30-mL multi-dose vial containing a clear, colorless to slightly yellow solution at a strength of 150 MBq/mL [4.05 mCi/mL] of flutemetamol F 18 at reference date and time.

4  CONTRAINDICATIONS
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)].

5  WARNINGS AND PRECAUTIONS
5.1 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)].

5.2 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 gray and white matter on a Vizamyl scan [see Dosage and Administration (2.3)]. 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.

5.3 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)].

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Clinical trials are conducted under widely varying conditions and adverse reaction rates observed in the clinical trials of Vizamyl cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. 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 185 MBq (5 mCi). One subject out of 761 administered Vizamyl experienced a serious hypersensitivity reaction with flushing, dyspnea and chest pressure within minutes following Vizamyl administration and recovered with treatment. Most adverse reactions were mild to moderate in intensity and resolved spontaneously. The most commonly reported adverse reactions occurring in at least 1% of subject in Vizamyl-treated subjects are shown in Table 2.
Table 2: Adverse Reactions Reported in Clinical Trials of Vizamyl (N = 761 subjects)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N (percent of patients)</th>
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</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>16 (2%)</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (1%)</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS
Pharmacodynamic drug-drug interaction studies have not been performed in patients to establish the extent, if any, to which concomitant medications may alter Vizamyl image results. Within a clinical study of patients with a range of cognitive impairment, some patients were receiving the following medications: donepezil, galantamine, memantine, rivastigmine. Mean cortical Standardized Uptake Value (SUV) ratios did not differ between the patients taking or not taking these concomitant medications.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: It is not known whether Vizamyl can cause fetal harm when administered to a pregnant woman or if it can affect reproduction capacity. Animal reproduction studies have not been conducted with Vizamyl. All radiopharmaceuticals, including Vizamyl, have the potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the magnitude of the radiopharmaceutical dose. Vizamyl should be given to a pregnant woman only if clearly needed. Assess pregnancy status before administering Vizamyl to a female of reproductive potential.

8.3 Nursing Mothers
It is not known whether flutemetamol is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for radiation exposure to nursing infants from Vizamyl, avoid use of the drug in a breastfeeding mother or have the mother temporarily interrupt breastfeeding for 24 hours (greater than 10 half-lives of radioactive decay for the F 18 isotope) after exposure to Vizamyl. If breastfeeding is interrupted, the patient should pump and discard her breast milk and use alternate infant nutrition sources (e.g., stored breast milk or infant formula) for 24 hours after administration of the drug.

8.4 Pediatric Use
Vizamyl is not indicated for use in pediatric patients.

8.5 Geriatric Use
Of the 761 subjects in clinical studies of Vizamyl, 447 (59%) were 65 years or over, while 246 (32%) were 75 years or over. No overall differences in safety were observed between these subjects and younger subjects.

10 OVERDOSAGE
The clinical consequence of overdose with Vizamyl has not been reported. It is unknown whether or not flutemetamol is dialyzable. The major risks of overdose relate predominantly to increased radiation exposure, with long-term risks for neoplasia. In case of overdose of radioactivity, hydration and frequent urination should be encouraged to minimize radiation exposure to the patient, care should be taken to avoid contamination from the radioactivity eliminated by the patient.

11 DESCRIPTION
Vizamyl contains flutemetamol F 18, a molecular imaging agent that binds to β-amyloid aggregates, and is intended for use with PET imaging of the brain. Chemically, flutemetamol F 18, is described as 2-(3-(18 F)fluoro-4-(methylamino)phenyl)-6-benzothiazolol. It has the molecular formula C 14 H 11 18 FN 2 OS, molecular weight 273.32, and the following structural formula:

![Vizamyl Structural Formula](image)

Vizamyl is a sterile, non-pyrogenic, clear, colorless to slightly yellow radioactive solution for intravenous injection. Each milliliter (mL) of the no-carrier added Vizamyl product solution contains 150 MBq (4.05 mCi) of flutemetamol F 18 at reference date and time and up to 2 micrograms of flutemetamol. Each mL of the Vizamyl solution also contains 70 microliters ethanol, 9.0 mg sodium chloride and 4.98 mg polysorbate 80 (w/v) in 0.014 M aqueous phosphate buffer. The pH of the solution is between 6.0 and 8.5.

11.1 Physical Characteristics
Fluorine-18 (F 18) is a cyclotron-produced radionuclide that decays by positron emission (β+ decay, 96.7%) and orbital electron capture (3.3%) to stable oxygen-18 with a physical half-life of 109.8 minutes. The positron can undergo annihilation with an electron to produce two gamma rays; the energy of each gamma ray is 511 keV (Table 3).

Table 3: Principal Radiation Emission Data – Fluorine-18

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Energy (keV)</th>
<th>Abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>511 × 193.4</td>
<td></td>
</tr>
<tr>
<td>Positron</td>
<td>249.8 × 96.7</td>
<td></td>
</tr>
</tbody>
</table>

11.2 External Radiation
The point source air-kerma rate constant for F-18 is 3.74E-17 Gy m²/(Bq s); this coefficient was formerly defined as the specific gamma-ray constant of 5.7 R/hr/MG at 1 cm. The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F-18 that results from various thicknesses of lead shielding is shown in Table 4. The use of ~8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.
12. Mechanism of Action
Flutemetamol F 18 binds to β-amyloid plaques in the brain and the F-18 isotope produces a positron signal that is detected by a PET scanner. In vitro binding studies using postmortem human brain homogenates containing fibrillar β-amyloid, the dissociation constant (K) for flutemetamol was 6.7 nM.

12. Pharmacodynamics
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 cortical areas that contain β-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 shows continual signal increases from time zero through 35 minutes post administration, with stable values thereafter up to at least 120 minutes post-injection. Differences in signal intensity between brain regions that specifically retain flutemetamol F 18 and brain regions with non-specific retention of the drug form the basis of image interpretation methods (see Dosage and Administration (2.5)).

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 185 MBq (5 mCi) of Vizamyl in humans, flutemetamol F 18 plasma concentrations declined by approximately 75% in the first 20 minutes post-injection, and by approximately 80% 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 was approximately 37% renal (28-45%; n=6) and 52% hepatobiliary (40-65%; n=6).

13. Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been performed to evaluate the carcinogenicity potential of flutemetamol. Flutemetamol was positive for mutagenicity in two in vitro assays: the bacterial reverse mutation assay (Ames test) and the mouse lymphoma assay.

Flutemetamol was negative for genotoxicity after in vivo exposure in rats to flutemetamol at the highest cumulative dose level tested, as measured in bone marrow micronucleus assays (157 and 27 microgram/kg/day for 2 and 14 days respectively) and an unscheduled DNA synthesis assay in rat hepatocytes (39 microgram/kg/day).

16. CLINICAL STUDIES
Vizamyl was evaluated in two clinical studies (Study One and Study Two) in adult subjects with a range of cognitive function, including some terminally ill patients who had agreed to participate in a post-mortem brain donation program. Both studies were single-arm and subjects underwent Vizamyl injection and scan. The imaging was interpreted by five independent readers masked to all clinical information; readers in Study Two were naïve to all forms of amyloid PET imaging. PET images were reviewed first without, and subsequently with, brain CT or MRI images.

Study One evaluated pre-mortem Vizamyl PET images from terminally ill patients and compared the results to postmortem truth standard assessments of cerebral cortical neuritic plaque density in patients who died after the study. 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. To determine the agreement between the in vivo Vizamyl images and the post-mortem whole brain amyloid neuritic plaque density, Vizamyl images (negative/positive) were pre-specified to correspond with specific global histopathology plaque density scores, based on a Registry for Alzheimer’s Disease (CERAD) criteria (Table 5), which use neuritic plaque counts as a necessary pathological feature of AD. Plaques were counted on microscopic 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, the subject’s brain was classified as positive for amyloid.
Vizamyl performance characteristics for Study One and Study Two patients with an autopsy-based truth standard are shown in Table 6 and Table 7. Among patients who underwent autopsy (n=68; 43 positive and 25 negative based on histopathology), the median (and range) of correct read results, false negatives, and false positives were 59 (51, 61), 5 (3, 8), 3 (2, 14), respectively, for in-person training (Study One); and were 60 (55 to 61), 3 (3 to 6), 4 (2 to 10), respectively, for electronic media training (Study Two). Image reproducibility for various subject groups in Study Two is presented in Table 8. 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 > 0.61). 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 29 images, two readers had discordant reads for a single image, and two readers had discordant reads for two images. Intra-reader reproducibility for a subgroup of 8 images from aMCI patients showed that all five readers had complete agreement for all duplicate images.

Table 6. Vizamyl Scan Results by Reader Training Method among Patients with Autopsy (n = 68)

<table>
<thead>
<tr>
<th></th>
<th>In-Person Training (Study One)</th>
<th>Electronic Media Training (Study Two)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity (%)</strong></td>
<td>Median</td>
<td>Range among the 5 readers</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>81 - 93</td>
</tr>
<tr>
<td></td>
<td><strong>Specificity (%)</strong></td>
<td>Range among the 5 readers</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>64 - 84</td>
</tr>
<tr>
<td></td>
<td><strong>False Negatives</strong></td>
<td>3 (2, 14)</td>
</tr>
<tr>
<td></td>
<td><strong>False Positives</strong></td>
<td>3 (2, 10)</td>
</tr>
</tbody>
</table>

Table 7. Vizamyl Scan Interpretations by Reader Training Method among Autopsied Patients (n = 68)

Table 8 (Study Two): Median Number of Positive Vizamyl Scans and Reproducibility of Scan Results

<table>
<thead>
<tr>
<th>Subject Group by Cognitive and Truth Standard (TS)</th>
<th>Positive Scans N</th>
<th>Kappa (95% CI)</th>
<th>Percent of Scans with Inter-reader Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 276 subjects</td>
<td>139</td>
<td>0.83 (0.79, 0.86)</td>
<td>5 of 5 readers agreed</td>
</tr>
<tr>
<td>All subjects with a TS, n=104 (48 autopsy, 36 biopsy)</td>
<td>58</td>
<td>0.74 (0.68, 0.80)</td>
<td>6 of 5 readers agreed</td>
</tr>
<tr>
<td>All subjects without a TS, n=172</td>
<td>76</td>
<td>0.88 (0.83, 0.92)</td>
<td>5 of 5 readers agreed</td>
</tr>
<tr>
<td>pAD, n = 63 (10 with TS; 53 no TS)</td>
<td>47</td>
<td>0.80 (0.78, 0.93)</td>
<td>4 of 5 readers agreed</td>
</tr>
<tr>
<td>aMCI, n = 80 (10 with TS)</td>
<td>45</td>
<td>0.80 (0.80, 0.88)</td>
<td>4 of 5 readers agreed</td>
</tr>
<tr>
<td>Elderly cognitively normal without TS, n = 28</td>
<td>5</td>
<td>0.64 (0.40, 0.84)</td>
<td>4 of 5 readers agreed</td>
</tr>
<tr>
<td>Cognitively normal with TS, n=12</td>
<td>10</td>
<td>0.83 (0.75, 0.91)</td>
<td>5 of 5 readers agreed</td>
</tr>
<tr>
<td>Other (non-AD) dementia with TS, n=5*</td>
<td>27</td>
<td>0.71 (0.63, 0.80)</td>
<td>8 of 5 readers agreed</td>
</tr>
</tbody>
</table>

* A dashed line indicates no median number of scans interpreted as positive across the 5 readers for each subgroup of subjects listed in the first column.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Vizamyl is supplied in a 10-mL or a 30-mL multi-dose glass vial with 1-10 mL and 1-30 mL fill volume respectively. Each vial is enclosed in an appropriate radiation shield. The total concentration is 150 MBq/mL (4.05 mCi/mL) of flutemetamol F 18 at reference date and time.

10-mL sterile multi-dose vial with variable fill volume: NDC 17156-067-10
30-mL sterile multi-dose vial with variable fill volume: NDC 17156-067-30

16.2 Storage

Store Vizamyl at 2° to 30°C (36° to 86°F). The product does not contain a preservative. Store Vizamyl within radiation shielding. Do not use Vizamyl after the expiry date and time stated on the label.

16.3 Handling

Vizamyl must not be diluted. This preparation is for use by persons licensed by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform their healthcare provider if they:
- are pregnant or breast feeding, or
- have had prior reactions to Vizamyl or any component, including polysorbate 80, or
- have reduced renal or hepatic function

Instruct patients to increase their level of hydration before and after receiving Vizamyl (Flutemetamol F 18 Injection) and to void frequently for the first 24 hours following Vizamyl administration.

GE Healthcare

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