

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIZAMYL 400 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 400 MBq of flutemetamol (^{18}F) at reference date and time.

The activity per vial may range from 400 MBq to 4000 MBq or from 400 MBq to 6000 MBq at the reference date and time.

Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of approximately 110 minutes by emitting a positron radiation of 634 keV, followed by photonic annihilation radiation of 511 keV.

Excipients with known effect

Each mL of solution contains 55.2 mg of ethanol and 4.1 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

VIZAMYL is a radiopharmaceutical medicinal product indicated for Positron Emission Tomography (PET) imaging of β -amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. VIZAMYL should be used in conjunction with a clinical evaluation.

A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD. For the limitations in the interpretation of a positive scan, see sections 4.4 and 5.1.

4.2 Posology and method of administration

A PET scan with flutemetamol (^{18}F) should be requested by clinicians experienced in the clinical management of neurodegenerative disorders.

VIZAMYL images should only be interpreted by readers trained in the interpretation of PET images with flutemetamol (^{18}F). A recent co-registered Computed Tomography (CT) scan or Magnetic Resonance (MR) scan of the patient to obtain a fused PET-CT or PET-MR image is recommended in cases of uncertainty about the location of grey matter and of the grey/white matter border in the PET scan (see section 4.4 Interpretation of VIZAMYL images).

Posology

Adults

The recommended activity for an adult is 185 MBq of flutemetamol (^{18}F) administered intravenously (as a bolus within approximately 40 seconds). The volume of the injection should be not less than 1 mL and not more than 10 mL.

Special populations

Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed.

Elderly patients

No dose adjustment is recommended based on age.

Renal and hepatic impairment

VIZAMYL has not been studied in patients with significant renal or hepatic impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients (see section 4.4). The pharmacokinetics of flutemetamol (^{18}F) in patients with renal or hepatic impairment has not been characterised.

Paediatric population

There is no relevant use of VIZAMYL in the paediatric population.

Method of administration

VIZAMYL is for intravenous use.

The activity of flutemetamol (^{18}F) has to be measured with a dose calibrator immediately prior to injection.

Injection of VIZAMYL through a short intravenous catheter (approximately 12.5 cm or less) minimises the potential for adsorption of the active substance to the catheter.

VIZAMYL is for multidose use. It must not be diluted.

The dose is administered by intravenous bolus injection within approximately 40 seconds. If using an intravenous line, follow the injection with an intravenous flush of 5 mL to 15 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose.

The injection of flutemetamol (^{18}F) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

Image acquisition

VIZAMYL images should be acquired starting 90 minutes after injection, using a PET scanner in 3D mode with appropriate data corrections. Position the patient supine with the patient's brain (including the cerebellum) within a single field of view. The patient's head should be tilted so that the anterior commissure-posterior commissure (ACPC) 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 4 mm, and an axial matrix size of 128 x 128 with pixel sizes of approximately 2 mm. Where a post-smoothing filter may be applied with a full width half maximum (FWHM) of not more than 5 mm, the filter FWHM should be chosen to optimize the signal-to-noise ratio while preserving the sharpness of the reconstructed image. The scan duration should typically be 20 minutes.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies the necessary medicinal products and equipment such as endotracheal tube and ventilator must be readily available.

Individual benefit/risk justification

For each patient, the radiation exposure must be justified by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information.

Renal /Hepatic impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. Flutemetamol (^{18}F) is excreted largely through the hepatobiliary system and patients with hepatic impairment have the potential of increased radiation exposure. See section 4.2.

Paediatric population

For information on the use in the paediatric population, see sections 4.2 or 5.1.

Interpretation of VIZAMYL images

VIZAMYL images should only be interpreted by readers trained in the interpretation of PET images with flutemetamol (^{18}F). A negative scan indicates none or a sparse density of cortical β -amyloid neuritic plaques. A positive scan indicates a moderate to frequent density. Image interpretation errors in the estimation of brain β -amyloid neuritic plaque density, including false negatives and false positives, have been observed.

PET images should be read using a Sokoloff, Rainbow or Spectrum colour scale. The reader should compare the cortical grey matter signal intensity to the maximum white matter signal intensity. The images should be viewed in a systematic manner (Figure 1) starting at the level of pons (p) and scrolling up through

- The frontal lobes and anterior cingulate (**f, ac**, axial review)
- Posterior cingulate and precuneus (**pc**, sagittal review)
- Temporo-parietal aspects including Insula (**in**, axial review and **tp-in**, coronal review)
- Lateral temporal lobes (**lt**, axial review)
- Striatal region (**s**, axial review)

Interpretation of the images is performed visually by comparing the activity in cortical grey matter with activity in adjacent cortical white matter.

- A region is considered as having a negative (normal) pattern if the tracer signal in cortical regions is low (i.e. distinctly lower signal intensity compared with adjacent white matter and similar in intensity to the grey matter-rich regions of the cerebellum). Signal will not be completely absent in grey matter regions of the images, as white matter binding in adjacent regions will bleed into the grey matter regions due to PET partial volume resolution effects.
- A region is considered positive (abnormal) if the tracer signal in cortical regions appears high (i.e., approximately at the same or higher signal intensity as adjacent white matter and greater than the grey matter-rich regions of the cerebellum).
- If any one of these regions is clearly positive (abnormal) then the image should be classified as positive (abnormal). Otherwise it should be classified as negative (normal).

Atrophy may be present in many areas of the brain and may render image interpretation more difficult as loss of grey matter will result in reduced tracer uptake making a positive scan more difficult to recognise. It is strongly recommended to review MR or CT images when available to aid interpretation of the VIZAMYL image, especially when atrophy is suspected.

Figure 1

VIZAMYL PET cases showing examples of negative flutemetamol (^{18}F) PET scan (left) and positive scan (right). Axial view (first row), sagittal view (second row) and coronal view (third row) are displayed.

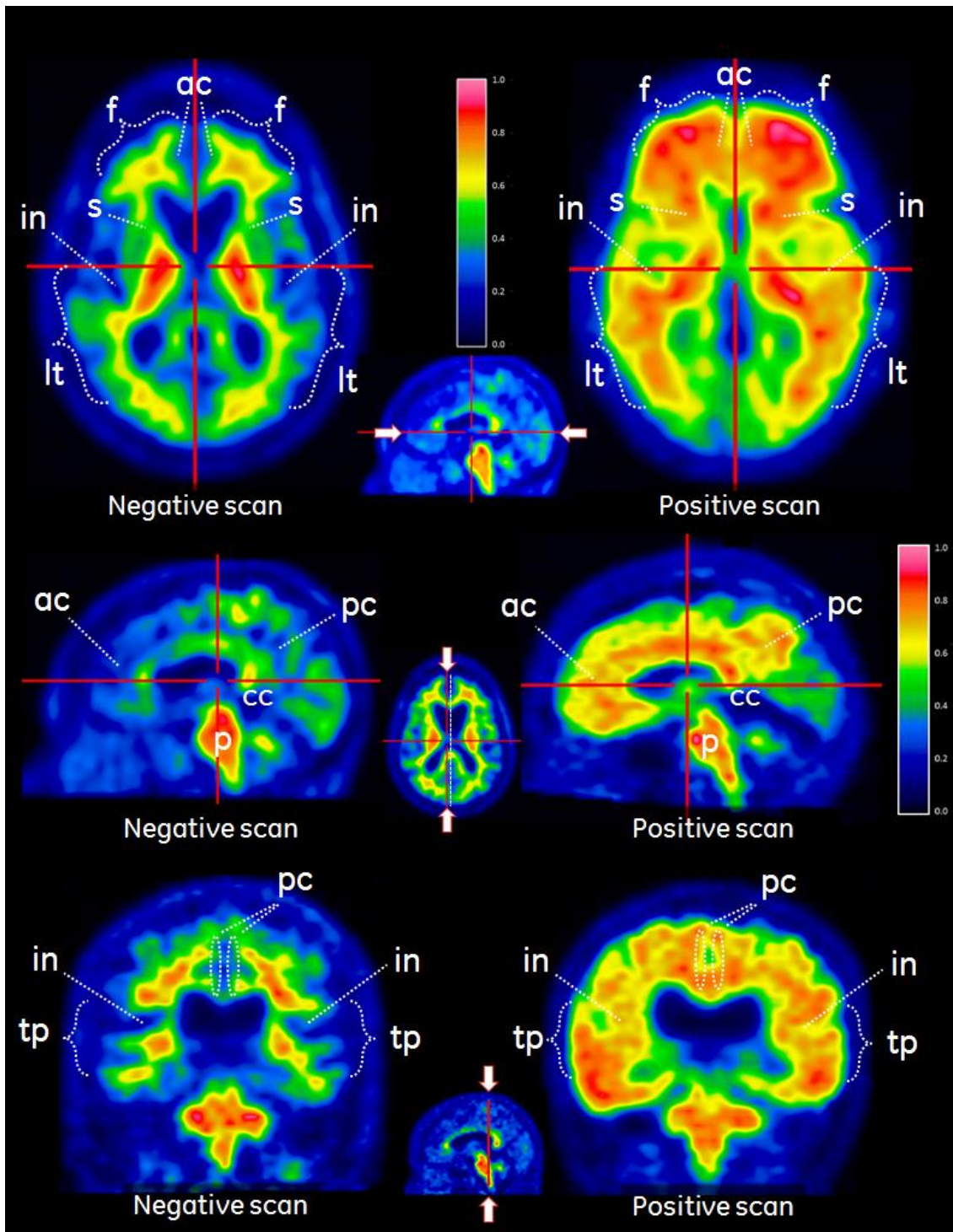


Figure 1. Axial (a), Sagittal (b) and coronal (c) views of a negative and positive flutemetamol (^{18}F) scans (left and right respectively). The negative images show a sulcal/gyral white matter pattern. The sulcal and gyral pattern is not discernible in the positive images on the right. Note that the intensity is higher ($> 60\%$ of max) in the grey matter regions of the positive images compared to the negative images and that the intensity radiates to a sharply defined convex edge in the lateral aspects. The negative images show a tapered intensity to the periphery of the tissue. Note also the medial regions where higher levels of intensity in the grey matter are seen in the positive images on the right.

Key: Grey matter – **f** frontal and **ac** anterior cingulate, **pc** posterior cingulate and precuneus, **lt** lateral temporal, **tp** temporo-parietal and **in** insula and **s** striatum. White matter – **p** pons and **cc** corpus callosum.

Quantitative assessment of cortical radioactive signal intensity using validated and CE marked computer software may be used to assist in the visual estimate of radioactive signal distribution. Such software provides a calculation of brain amyloid load by dividing the mean image intensity in the cortical regions associated with amyloid deposition (raised in AD subjects) with the mean image intensity in a reference region such as the pons. The measure is referred to as Standard Uptake Value ratio or SUVR. Dichotomous visual reads for flutemetamol (18F) scans were validated against the boundary between sparse and moderate neuritic plaque densities. An SUVR threshold value of 0.59 to 0.61 derived from CE marked software using the pons as a reference has been determined to give very high concordance with visual reads (see section 5.1) and may be used as an adjunct to visual reading.

Users should be trained in the use of CE marked software by the manufacturer and should have completed the reader training for the visual interpretation of Vizamyl images.

In case of discordance of visual read and quantitation result, the following steps should be carefully considered to come to a final assessment.

Readers should interpret the scan visually and then perform quantitation analysis according to manufacturer's instructions including quality checks for the quantitation process. The results of quantitation should be compared to the visual interpretation, paying attention to the expected ranges for a negative or positive scan. If the quantitation values are inconsistent with the visual interpretation, the reviewer should:

1. Check the placement of the regions of interest (ROIs) on the brain image. The regions should be placed on the grey matter regions of the brain such that the ROIs do not include CSF or significant areas of white matter.
2. Examine the placement of the reference region ROI(s) to ensure that these are well fitted to the region. Secondly, examine the appearance of the reference region looking for any structural abnormalities or areas of reduced perfusion.
3. Specifics of opposing visual and quantitative results
 - i) In the case of an amyloid positive visual read and an amyloid negative or borderline quantitative result, a comparison should be made between the regions showing visual positivity and the equivalent area sampled by a ROI. In the case where tracer uptake is highly focal, it may be that the ROI samples a larger area and the average of the ROI returns a negative result. Further, a visual read may be conducted in such a way as to avoid atrophied regions, while quantitation may include these areas.
 - ii) In the case of an amyloid negative visual read and a positive quantitative result, the reference region should be inspected and where any concerns on ROI placement accuracy or reduced uptake are evident, an alternative region should be used (the software may allow for a number of different reference regions). Further, the placement of the cortical ROIs should be checked to determine if white matter is sampled, which may increase quantitation values.
4. A final interpretation of the PET image should be made on the basis of the visual read having conducted the review outlined in steps 1 to 3.

Limitations of use

A positive scan does not independently establish a diagnosis of AD or other cognitive disorder since neuritic plaque deposition in grey matter may be present in asymptomatic elderly patients and some neurodegenerative dementias (Alzheimer's disease, but also Lewy body dementia and Parkinson's disease dementia).

For the limitations of use in patients with mild cognitive impairment (MCI), see section 5.1.

The efficacy of flutemetamol (¹⁸F) for predicting development of AD or monitoring response to therapy has not been established (see section 5.1).

Some scans may be difficult to interpret due to image noise, atrophy with a thinned cortical ribbon or image blur, which could lead to interpretation errors. For cases in which there is uncertainty about the location of grey matter and of the grey/white matter border on the PET scan, and a co-registered recent CT or MR image is available, the interpreter should examine the fused PET-CT or PET-MR image to clarify the relationship of the PET radioactivity and the grey matter anatomy.

After the procedure

Close contact with infants and pregnant women should be restricted during the initial 24 hours following the injection.

Specific warnings

This medicinal product contains (7 vol %) of ethanol (alcohol), i.e. up to 552 mg (approximately 0.7 mL) per dose. This amount may be harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women and high-risk groups such as patients with liver disease or epilepsy.

This medicinal product contains up to 41 mg (or 1.8 mmol) sodium per dose, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. This may need to be taken into consideration by patients on a controlled sodium diet.

For precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic drug-drug interaction studies have not been performed in patients to establish the extent, if any, to which concomitant medicinal products may alter VIZAMYL image results.

No *in vivo* interaction studies have been performed.

In vitro binding studies have not shown interference of flutemetamol (¹⁸F) binding to β -amyloid plaques in the presence of other common medicinal products taken by AD patients.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

No studies have been conducted in pregnant women. No animal studies have been conducted to investigate the reproductive effects of flutemetamol (¹⁸F) (see section 5.3).

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

Breast-feeding

It is not known whether flutemetamol (¹⁸F) is excreted in human milk during breast-feeding. Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and to the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for 24 hours and the expressed feeds discarded.

Close contact with infants should be restricted during the initial 24 hours following injection.

Fertility

No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

VIZAMYL has no or negligible influence on the ability to drive and use machines.

However, VIZAMYL may cause transient dizziness and vertigo. Therefore, following the administration of VIZAMYL, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until these effects have completely disappeared.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of VIZAMYL is based on data from its administrations to 831 subjects.

Tabulated list of adverse reactions

The frequencies of adverse reactions are defined as follows:

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The following adverse reactions are listed in the Table 1 below:

Table 1 List of adverse reactions

System Organ Class	Common	Uncommon
Immune system disorders		Anaphylactoid reaction
Psychiatric disorders		Anxiety
Nervous system disorders		Dizziness Headache Hypoaesthesia Hypotonia Dysgeusia Tremor
Eye disorders		Eye swelling
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Palpitations
Vascular disorders	Flushing	Pallor
Respiratory, thoracic and mediastinal disorders		Dyspnoea Hyperventilation Throat irritation
Gastrointestinal disorders		Nausea Vomiting Dyspepsia Abdominal discomfort Oral discomfort
Skin and subcutaneous tissue disorders		Facial hypoaesthesia Pruritus Rash Skin tightness Swelling face
Musculoskeletal and connective tissue disorders		Back pain Muscle tightness Musculoskeletal pain
Reproductive system and breast disorders		Erectile dysfunction
General disorders and administration site conditions		Chest discomfort Feeling hot Asthenia Fatigue Feeling abnormal Feeling cold Infusion site pain Oedema Pyrexia
Investigations	Increased blood pressure	Blood glucose decreased Blood lactate dehydrogenase increased Neutrophil count increased Respiratory rate increased

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. The effective dose is approximately 5.9 mSv when the maximal recommended activity of 185 MBq of flutemetamol (¹⁸F) is administered. These adverse events are expected to occur with low probability.

Description of selected adverse reactions

The following adverse reactions may occur as symptoms and signs of a hypersensitivity reaction to VIZAMYL or any of its excipients (see section 6.1): eye/face swelling, pallor, dyspnoea, throat irritation, vomiting, rash, pruritus, skin tightness, chest tightness (see also section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Due to the small quantity of flutemetamol (^{18}F) in each dose, overdose is not expected to result in pharmacological effects. In the event of administration of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defecation. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical, central nervous system,
ATC code: V09AX04

Mechanism of action

Flutemetamol (^{18}F) binds to β -amyloid neuritic plaques in the brain.

In vitro, flutemetamol (^{18}F) binds to β -amyloid neuritic plaques in the brain, with negligible binding to neurofibrillary tangles. Data suggest that flutemetamol (^{18}F) is able to label cored and diffuse amyloid β deposits and neuritic plaques. There is no evidence of flutemetamol (^{18}F) binding to soluble forms of A β .

In vivo, quantitative correlation was assessed in end-of-life patients between flutemetamol (^{18}F) uptake in cortical grey matter and the total β -amyloid burden in autopsied samples using 4G8 anti-amyloid antibody that stains β -amyloid found in both neuritic and diffuse plaques. *In vivo*, flutemetamol (^{18}F) can detect β -amyloid diffuse plaques when they are frequent. The *in vivo* binding of flutemetamol (^{18}F) to other β -amyloid structures or other brain structures or receptors remains unknown.

Pharmacodynamic effects

At the low concentrations present in VIZAMYL, flutemetamol (^{18}F) has no detectable pharmacodynamic activity.

Brain uptake and distribution of flutemetamol (^{18}F) were not evaluated in a specific study aimed to evaluate pharmacodynamics. In two similar studies of biodistribution and a phase II clinical study, mean quantitative uptake values in PET images differed between pAD and HV subjects in most examined areas of the brain.

Clinical efficacy

A pivotal study in 68 end-of-life patients was aimed at establishing the diagnostic performance of flutemetamol (^{18}F) to detect the cortical neuritic plaque density. The PET results were compared with the neuritic plaque density measured on sections of eight predefined brain regions at the patient's autopsy. The histopathology regions included, but were not restricted to the CERAD regions. The cognitive status of the patients was not determined. In the 68 patients, a blinded visual patient-level PET read by 5 blinded readers resulted in a majority read sensitivity of 86% (95% CI: 72% to 95%) and specificity 92% (95% CI: 74% to 99%).

Sensitivity and specificity to estimate β -amyloid deposition of flutemetamol (^{18}F) was further investigated in one additional study, in which a different set of 5 electronically-trained blinded readers interpreted images from the same 68 patients followed to autopsy in the pivotal study. Histopathology

from the pivotal study was used. The majority read sensitivity and specificity were 93% (95% CI: 81% to 99%) and 84% (95% CI: 64% to 96%), respectively.

In a re-reading study that increased the patient population of the pivotal study to include 38 additional autopsied patients (i.e., 106 in total), sensitivity and specificity for detection of moderate-frequent β -amyloid neuritic plaque density in the primary analysis were 91% (95% CI: 82% to 96%) and 90% (95% CI: 74% to 98%), respectively, based on the majority read (i.e., the image interpretation reached by at least 3 of the 5 readers after electronic training). In a secondary analysis that used a standard of truth based on the region of maximum neuritic plaque involvement in the 3 neocortical regions originally recommended by CERAD, sensitivity was 92% (95% CI: 83% to 97%), and specificity was 88% (95% CI: 71% to 97%).

In a longitudinal study, 232 patients clinically diagnosed with amnesic mild cognitive impairment (aMCI), underwent baseline flutemetamol (^{18}F) PET scans, and were followed for 36 months to evaluate the relationship between flutemetamol (^{18}F) imaging and changes in diagnostic status. 98 (42%) of the 232 patients had abnormal (positive) flutemetamol (^{18}F) scans. Of the 232 patients enrolled, 224 had at least one post-scan review by the independent committee and were included in the analysis. At the 36-month follow-up, 81 (35%) converted to clinical AD. Of the 97 aMCI patients who had a positive PET scan and at least one committee assessment, 52 (54%) were classified clinically as converted to clinical AD after 36 months compared to 29 (23%) of 127 who had a negative scan and at least one committee assessment. At 36 months, sensitivity of flutemetamol (^{18}F) scans for predicting conversion from aMCI to AD in 81 converters was 64 % (95% CI: 54% to 75 %), specificity in 143 non-converters was 69% (95% CI: 60% to 76 %). Based on the majority read, the positive and negative likelihood ratios were 2.04 and 0.52 respectively. The design of this study does not allow estimating the risk of MCI progression to clinical AD.

Clinical Studies demonstrating adjunctive use of quantitative information for image interpretation

The reliability of using quantitative information as an adjunct to visual inspection was analysed in two clinical studies where the concordance between the two methods of image interpretation were compared. In both studies (total n=379) CE marked amyloid quantitation software was used and the % agreement between visual reads and quantitation was 98.8% to 99%. In study one, the thresholds for amyloid quantitation were calculated against post-mortem confirmation of brain amyloid status as the standard of truth (from pivotal clinical autopsy cohort n=68) and a healthy cohort of n=105 volunteers used to define the reference range for normal quantitative measures. The derived thresholds were used to categorise a test cohort of 172 scans (33 probable AD, 80 amnesic MCI and 59 healthy volunteers) as negative or positive and compared to categorisation by visual read. Agreement was 98.8% (170/172 scans).

In the second study, to investigate the impact of amyloid PET with flutemetamol (^{18}F) on diagnosis and treatment management in a cohort of patients attending a tertiary memory clinic, 207 patients had images interpreted by visual inspection or CE marked software with an agreement of 99% (205/207 scans) between the two methods..

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with flutemetamol (^{18}F) in all subsets of the paediatric population as the disease or condition for which the specific medicinal product is intended only occurs in adults (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution

Flutemetamol (^{18}F) is distributed throughout the body within several minutes of injection. After 20 minutes approximately 20 % of the active compound flutemetamol (^{18}F) remains in the circulation, falling to 10 % at 180 minutes.

Organ uptake

Maximal flutemetamol (^{18}F) brain uptake of approximately 7% of an injected dose occurs within two minutes of administration. This is followed by rapid clearance from the brain in the first 90 minutes (the recommended time to start scanning), followed by more gradual clearance. The five organs/tissues with the highest cumulated activities were the wall of the small intestines, liver, urinary bladder wall, wall of the upper large intestine and the wall of the gallbladder.

Healthy controls show low levels of flutemetamol (^{18}F) retention in cerebral cortex. The highest level of uptake is in pons and other white matter regions. In AD patients, cortical regions and striatal regions show significantly greater uptake compared to cortical regions in controls. In AD patients, as in controls, there is high retention in pons and other white matter areas.

The biophysical basis of the white matter retention of flutemetamol (^{18}F) in the living human brain has not been definitively explained. It is hypothesized that solubility of the radiopharmaceutical in the lipid content of brain tissues may contribute to white matter retention.

Elimination and half-Life

Flutemetamol (^{18}F) is rapidly cleared from circulation (through the intestinal and urinary tracts). At 20 minutes post-injection, 75% of the radioactivity in plasma was present as polar metabolites. At 180 minutes, 90% of the radioactivity was present in plasma in the form of polar metabolites. Elimination of flutemetamol (^{18}F) is approximately 37% renal and 52% hepatobiliary. The apparent elimination half-life is 4.5 hours whereas the radioactive half-life of flutemetamol (^{18}F) is 110 minutes.

Renal/hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment have not been characterised.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Flutemetamol (^{18}F) was positive in *in vitro* genotoxicity tests in bacteria and mammalian cells but negative in three different *in vivo* studies with sufficiently high doses. Any clinically relevant mutagenic potential is therefore considered highly unlikely.

No carcinogenicity and reproductive toxicology studies have been performed with flutemetamol (^{18}F).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Ethanol, anhydrous
Polysorbate 80
Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate dodecahydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Eight hours from the reference date and time.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

VIZAMYL is supplied in 10-mL and 15-mL Type I glass vials with halobutyl rubber stoppers and aluminium seals.

As a result of the manufacturing process some vials are distributed with punctured rubber stoppers.

Pack size

One multidose vial of 10-mL capacity contains 1 to 10 mL of solution, corresponding to 400 to 4000 MBq at reference date and time.

One multidose vial of 15-mL capacity contains 1 to 15 mL of solution, corresponding to 400 to 6000 MBq at reference date and time.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper. The solution should then be withdrawn via the stopper, using either a single-dose syringe fitted with suitable protective shielding and a disposable sterile needle, or an authorised automated application system. If the integrity of the vial is compromised, the medicinal product should not be used.

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner that satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

VIZAMYL is a radioactive medicinal product that emits positrons, which annihilate with electrons to produce gamma rays, and must be handled with safety measures to minimise radiation exposure to clinical personnel and patients. VIZAMYL should be used by, or under the control of, physicians who are qualified by specific training and experienced in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate government agency authorised to license the use of radiopharmaceuticals. To minimise radiation dose to the bladder, hydration before and after VIZAMYL administration should be encouraged in order to permit frequent voiding. The patient should be encouraged to void prior to and following imaging with VIZAMYL, and frequently thereafter for the next 24 hours.

If at any time in the preparation of this product the integrity of the vial is compromised, it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must be taken.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/941/001
EU/1/14/941/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2014
Date of latest renewal: 25 July 2019

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

Table 2 below shows the dosimetry as calculated using the OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modeling) software. The estimated absorbed radiation doses for adults following intravenous injection of VIZAMYL are shown in Table 2. Values were calculated assuming emptying of the urinary bladder at 3.5-hour intervals and human biodistribution data using OLINDA/EXM software.

Table 2 Estimated radiation absorbed doses from intravenous injection of VIZAMYL (adults)

Organ/Tissue	Dose absorbed per activity administered [mGy/MBq]
Adrenal	0.013
Brain	0.011
Breasts	0.005
Gallbladder	0.287
Heart	0.014
Kidneys	0.031
Liver	0.057
Lower large intestine wall	0.042
Lungs	0.016
Muscles	0.009
Osteogenic cells	0.011
Ovaries	0.025
Pancreas	0.015
Red marrow	0.013
Skin	0.005

Small intestine	0.102
Spleen	0.015
Stomach	0.012
Testes	0.008
Thymus	0.006
Thyroid	0.006
Upper large intestine	0.117
Bladder	0.145
Uterus	0.025
Remaining organs	0.012
Effective dose (mSv/MBq)	0.032

The adult effective dose resulting from the administration of a maximal recommended activity of 185 MBq dose for an adult weighing 70 kg is approximately 5.9 mSv. For an administered activity of 185 MBq the typical radiation dose to the target organ (brain) is 2.0 mGy. If a CT scan is simultaneously performed as part of the PET procedure, exposure to ionising radiation will increase in an amount dependent on the settings used in the CT acquisition.

For an administered activity of 185 MBq the typical radiation doses delivered to the critical organs, gallbladder, urinary bladder wall, upper large intestine wall, lower large intestine wall, small intestine and liver are 53.1 mGy, 26.8 mGy, 21.6 mGy, 7.8 mGy, 18.9 mGy and 10.5 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation

The package must be checked before use and the activity measured using a dose calibrator.

See special handling precautions in section 6.6.

Flutemetamol (¹⁸F) must not be diluted.

Quality control

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 6.6).

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

AAA, Troyes
Advanced Accelerator Applications
Technopole de l'Aube
14 rue Gustave Eiffel
10430 Rosières près Troyes
France

AAA, Forli
Advanced Accelerator Applications S.r.l
Via Piero Maroncelli 40
47014 Meldola (FC)
Italy

Curium PET France
Parc scientifique Georges Besse
180 allée Von Neumann
30000 Nimes
France

Curium Italy S.R.L.
Via Ripamonti 435
20141 Milano (MI)
Italy

Curium Pharma Spain, S.A.,
C/Manuel Bartolome Cossio 10
28040 Madrid
Spain

Seibersdorf Laboratories, Seibersdorf
Seibersdorf Labor GmbH
Grundstück Nr. 482/2 EZ98 KG
2444 Seibersdorf
Austria

AAA, Zaragoza
Advanced Accelerator Applications Ibérica S.L.
Polígono Industrial la Cuesta 3, Parcelas 1 y 2
50100 La Almunia de Doña Godina
Zaragoza
Spain

AAA, Barcelona
Advanced Accelerator Applications Iberica S.L.U.
Josep Anselm Clavé 100
Esplugues de Llobregat
Barcelona, 08950
Spain

Nucleis SA
Allée du Six-Août, 8
4000 Liège
Belgium

MAP, Helsinki
MAP Medical Technologies Oy
Saukonpaadenranta 2
Helsinki, FI-00180
Finland

ITEL, Ruvo di Puglia
ITEL Telecomunicazioni S.r.l.
Via Antonio Labriola Zona Industriale SNC,
70037, Ruvo di Puglia (BA)
Italy

Helmholtz-Zentrum Dresden-Rossendorf e.V.
Zentrum für Radiopharmazeutische Tumorforschung
Bautzner Landstraße 400
01328 Dresden
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational programme with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where VIZAMYL is marketed, at launch and after launch, all physicians who are expected to use VIZAMYL have access to a training course in order to ensure accurate and reliable interpretation of the PET images.

The training course for healthcare professionals should contain the following key elements:

- Information on amyloid pathology in Alzheimer Disease; relevant information on VIZAMYL as an β -amyloid PET tracer, including the approved indication according to the SmPC, limitations of VIZAMYL use, interpretation errors, safety information and the results of clinical trials informing on the diagnostic use of VIZAMYL.
- Review of the PET reading criteria, including method of image review, criteria for interpretation, and images demonstrating the binary read methodology.
- The material should include VIZAMYL PET demonstration cases with correct PET scan interpretation by an experienced reader; VIZAMYL-PET scans for self-assessment; and a self-qualification procedure to be offered to each trainee. Training should include a sufficient number of clearly positive and negative cases as well as intermediate level cases. Cases should be histopathologically confirmed, if possible.

Expertise and qualification of trainers in both electronic and in-person training should be ensured.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SHIELD LABEL / 10 mL

1. NAME OF THE MEDICINAL PRODUCT

VIZAMYL 400 MBq/mL solution for injection
flutemetamol (¹⁸F)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains flutemetamol (¹⁸F) 400 MBq at reference date and time.

3. LIST OF EXCIPIENTS

Excipients: ethanol anhydrous, polysorbate 80, sodium chloride, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Volume: xx.x mL
Activity: 400 MBq/mL at {hh:mm} {Time Zone} on {dd-mm-yyyy}
Activity: YYYY MBq at hh:mm {Time Zone} dd-mm-yyyy

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Multidose vial
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Radioactive medicine



8. EXPIRY DATE

EXP: {hh:mm} {Time Zone} on {dd-mm-yyyy}

9. SPECIAL STORAGE CONDITIONS

Storage in accordance with national regulation on radiopharmaceuticals.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

Manufacturers:

Advanced Accelerator Applications, 47014 Meldola (FC), Italy

Advanced Accelerator Applications, Technopole de l'Aube, 10430 Rosières près Troyes, France

Seibersdorf Labor GmbH, 2444 Seibersdorf, Austria

Curium Pharma Spain, S.A., 28040 Madrid, Spain

Curium PET France, 30000 Nimes, France

Curium Italy S.R.L., 20141 Milano (MI), Italy

Advanced Accelerator Applications, 50100 La Almunia de Doña Godina, Zaragoza, Spain

Advanced Accelerator Applications Iberica S.L.U., Josep Anselm Clavé 100, 08950 Barcelona, Spain

Nucleis SA, Allée du Six-Août, 8, 4000 Liège, Belgium

MAP Medical Technologies, Saukonpaadenranta 2, 00180 Helsinki, Finland

ITEL Telecomunicazioni, Via Antonio Labriola Zona Industriale SNC, 70037, Ruvo di Puglia, Italy

Helmholtz-Zentrum Dresden-Rossendorf e.V., Zentrum für Radiopharmazeutische Tumorforschung, Bautzner Landstraße 400, 01328 Dresden, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/941/001

13. BATCH NUMBER

Lot:
Vial No: xxx

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SHIELD LABEL / 15 mL

1. NAME OF THE MEDICINAL PRODUCT

VIZAMYL 400 MBq/mL solution for injection
flutemetamol (¹⁸F)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains flutemetamol (¹⁸F) 400 MBq at reference date and time.

3. LIST OF EXCIPIENTS

Excipients: ethanol anhydrous, polysorbate 80, sodium chloride, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Volume: xx.x mL
Activity: 400 MBq/mL at {hh:mm} {Time Zone} on {dd-mm-yyyy}
Activity: YYYY MBq {at hh:mm} {Time Zone} on {dd-mm-yyyy}

5. METHOD AND ROUTE(S) OF ADMINISTRATION

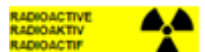
Intravenous use.
Multidose vial
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Radioactive medicine



8. EXPIRY DATE

EXP: {hh:mm} {Time Zone} on {dd-mm-yyyy}

9. SPECIAL STORAGE CONDITIONS

Storage in accordance with national regulation on radiopharmaceuticals.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

Manufacturers:

Advanced Accelerator Applications, 47014 Meldola (FC), Italy

Advanced Accelerator Applications, Technopole de l'Aube, 10430 Rosières près Troyes, France

Seibersdorf Labor GmbH, 2444 Seibersdorf, Austria

Curium Pharma Spain, S.A., 28040 Madrid, Spain

Curium PET France, 30000 Nimes, France

Curium Italy S.R.L., 20141 Milano (MI), Italy

Advanced Accelerator Applications, 50100 La Almunia de Doña Godina, Zaragoza, Spain

Advanced Accelerator Applications Iberica S.L.U. , Josep Anselm Clavé 100, 08950 Barcelona, Spain

Nucleis SA, Allée du Six-Août, 8, 4000 Liège, Belgium

MAP Medical Technologies, Saukonpaadenranta 2, 00180 Helsinki, Finland

ITEL Telecomunicazioni, Via Antonio Labriola Zona Industriale SNC , 70037, Ruvo di Puglia, Italy

Helmholtz-Zentrum Dresden-Rossendorf e.V., Zentrum für Radiopharmazeutische Tumorforschung, Bautzner Landstraße 400, 01328 Dresden, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/941/002

13. BATCH NUMBER

Lot:
Vial No: xxx

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL / 10 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VIZAMYL 400 MBq/mL solution for injection
flutemetamol (¹⁸F)
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP: reference time +8 h

4. BATCH NUMBER

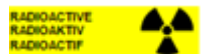
Lot:
Vial No: xxx

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

xx.x mL YYYY MBq at reference time

6. OTHER

Radioactive material.



Advanced Accelerator Applications, 47014 Meldola (FC), Italy

Advanced Accelerator Applications, Technopole de l'Aube, 10430 Rosières près Troyes, France

Seibersdorf Labor GmbH, 2444 Seibersdorf, Austria

Curium Pharma Spain, S.A., 28040 Madrid, Spain

Curium PET France, 30000 Nimes, France

Curium Italy S.R.L., 20141 Milano (MI), Italy

Advanced Accelerator Applications, 50100 La Almunia de Doña Godina, Zaragoza, Spain

Advanced Accelerator Applications Iberica S.L.U., Josep Anselm Clavé 100, 08950 Barcelona, Spain

Nucleis SA, 4000 Liège, Belgium

MAP Medical Technologies, Saukonpaadenranta 2, 00180 Helsinki, Finland

ITEL Telecomunicazioni, Via Antonio Labriola Zona Industriale SNC, 70037, Ruvo di Puglia, Italy

Helmholtz-Zentrum Dresden-Rossendorf e.V., Zentrum für Radiopharmazeutische Tumorforschung,
01328 Dresden, Germany

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL / 15 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VIZAMYL 400 MBq/mL solution for injection
flutemetamol (¹⁸F)
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP: reference time + 8h

4. BATCH NUMBER

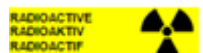
Lot:
Vial No: xxx

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

xx.x mL YYYY MBq at reference time.

6. OTHER

Radioactive material.



Advanced Accelerator Applications, 47014 Meldola (FC), Italy

Advanced Accelerator Applications, Technopole de l'Aube, 10430 Rosières près Troyes, France

Seibersdorf Labor GmbH, 2444 Seibersdorf, Austria

Curium Pharma Spain, S.A., 28040 Madrid, Spain

Curium PET France, 30000 Nimes, France

Curium Italy S.R.L., 20141 Milano (MI), Italy

Advanced Accelerator Applications, 50100 La Almunia de Doña Godina, Zaragoza, Spain

Advanced Accelerator Applications Iberica S.L.U., Josep Anselm Clavé 100, 08950 Barcelona, Spain

Nucleis SA, 4000 Liège, Belgium

MAP Medical Technologies, Saukonpaadenranta 2, 00180 Helsinki, Finland

ITEL Telecomunicazioni, Via Antonio Labriola Zona Industriale SNC, 70037, Ruvo di Puglia, Italy

Helmholtz-Zentrum Dresden-Rossendorf e.V., Zentrum für Radiopharmazeutische Tumorforschung,
01328 Dresden, Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

VIZAMYL 400 MBq/mL solution for injection flutemetamol (¹⁸F)

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise your procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VIZAMYL is and what it is used for
2. What you need to know before VIZAMYL is used
3. How VIZAMYL is used
4. Possible side effects
5. How VIZAMYL is stored
6. Contents of the pack and other information

1. What VIZAMYL is and what it is used for

VIZAMYL contains the active substance flutemetamol (¹⁸F) and is used to help diagnose Alzheimer's disease and other causes of memory loss.

This medicine is a radiopharmaceutical product for diagnostic use only.

VIZAMYL is used to help diagnose Alzheimer's disease and other causes of memory loss. It is given to adults with memory problems before they undergo a type of brain scan called a positron-emission tomography (PET) scan. This scan, along with other brain function tests, can help your doctor determine whether or not you may have β -amyloid plaques in your brain. β -Amyloid plaques are deposits sometimes present in the brains of people with dementias (such as Alzheimer's disease).

You should discuss the results of the test with the doctor that requested the scan.

The use of VIZAMYL involves exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit of this procedure with the radiopharmaceutical outweighs the risk of being exposed to these small amounts of radiation.

2. What you need to know before VIZAMYL is used

VIZAMYL must not be used:

- If you are allergic to flutemetamol (¹⁸F) or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your nuclear medicine doctor before you are given VIZAMYL if you:

- have kidney problems
- have liver problems
- are pregnant or think you may be pregnant
- are breast-feeding

Children and adolescents

VIZAMYL is not intended for use in children and adolescents below the age of 18 years old.

Other medicines and VIZAMYL

Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines since they may interfere with the images obtained from the brain scan.

Pregnancy and breast-feeding

You must inform the nuclear medicine doctor before you are given VIZAMYL if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding. When in doubt, it is important to consult the nuclear medicine doctor who will supervise the procedure.

If you are pregnant

The nuclear medicine doctor will only give this medicine during pregnancy if a benefit is expected which would outweigh the risks.

If you are breast-feeding

You must stop breast-feeding for 24 hours after the injection. Express the breast milk during this period and discard any breast milk you have expressed. Resuming breast-feeding should be in agreement with the nuclear medicine doctor who will supervise the procedure.

You should avoid any close contact with young children for 24 hours following the injection.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine.

Driving and using machines

VIZAMYL may cause transient dizziness or vertigo, which may affect your ability to drive or use machines. You should not drive, use machines or engage in other potentially hazardous activities until these effects have completely disappeared.

VIZAMYL contains alcohol (ethanol) and sodium

VIZAMYL contains alcohol (ethanol). Each dose contains up to 552 mg alcohol. This is about the same as 14 mL of beer or 6 mL of wine. This could be harmful for people with alcoholism and needs to be taken into account in pregnant or breast-feeding women and people with liver problems or epilepsy.

VIZAMYL contains a maximum of 41 mg of sodium (main component of cooking/table salt) in each dose. This is equivalent to approximately 2% of the adult recommended maximum daily dietary intake for sodium. These amounts may need to be considered for people on a low sodium diet.

3. How VIZAMYL will be used

There are strict laws on the use, handling and disposal of radiopharmaceutical products.

VIZAMYL will only be used in special controlled areas. This product will only be handled and given to you by professionals who are trained and qualified to use it safely. They will provide you with the necessary information on the procedure.

Your nuclear medicine doctor may ask you to drink plenty of water before the start of the examination and the 24 hours after the study in order to urinate as often as possible to help remove it from your body faster.

Dose

The nuclear medicine doctor supervising the procedure will decide on the amount of VIZAMYL to be used in your case. The doctor will choose the smallest amount necessary.

The usual amount recommended for an adult is 185 MBq. Megabecquerel (MBq) is the unit used to measure radioactivity.

Administration of VIZAMYL and conduct of the procedure

VIZAMYL is given as an injection into your vein (intravenous injection) followed by a flush of sodium chloride solution to ensure full delivery of the dose.

One injection is sufficient to carry out the scan that your doctor needs.

Duration of the procedure

A brain scan is usually taken 90 minutes after VIZAMYL is given. Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of VIZAMYL

You should avoid any close contact with young children and pregnant women for 24 hours following the injection.

The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

If you have received more VIZAMYL than you should

An overdose is unlikely since you will only receive a single dose of VIZAMYL from the nuclear medicine doctor under controlled conditions.

However, in the case of an overdose, you would receive the appropriate treatment. Treatment consists of increasing the passing of urine and stools in order to help remove radioactivity from your body.

If you have any further questions on the use of this medicine, please ask your nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Serious side effects

Tell your doctor straight away, if you notice any of the following, as you may need urgent medical treatment:

- Allergic reactions - the signs may include swelling of your face or eyes, having pale, itchy or tight skin or having a rash, feeling short of breath, tightness in the chest, irritation in your throat or being sick. These are uncommon side effects and may affect up to 1 in 100 people.

Tell your doctor straight away if you notice any of the signs above.

Other side effects include

Common - may affect up to 1 in 10 people

- looking flushed
- increased blood pressure

Uncommon - may affect up to 1 in 100 people. You may experience the following uncommon side effects:

- headache
- feeling dizzy
- feeling anxious
- feeling sick (nausea)
- chest discomfort
- low blood sugar (symptoms: hunger, headache)

- back pain
- feeling hot or cold
- increased breathing rate
- pain at the injection site
- heart pounding (palpitations)
- pain in muscles or bones
- shaking movements (tremor)
- puffy and swollen skin
- fever
- over breathing (hyperventilation)
- change in the way you taste things
- a spinning feeling (vertigo)
- reduced sense of touch or sensation
- feeling tired or weak
- inability to get or maintain an erection
- indigestion, stomach ache or sore mouth
- vomiting
- decreased feeling or sensitivity especially in your skin or your face
- increase in “blood lactate dehydrogenase” or “neutrophils” in blood tests
- skin tightness

This radiopharmaceutical will deliver low amounts of ionising radiation, which is associated with very low risk of cancer and hereditary abnormalities (passing on faulty genes).

Reporting of side effects

If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How VIZAMYL is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

The following information is intended for the specialist only.

Do not use this medicine after the expiry date and time, which are stated on the label after ‘EXP’.

Do not use this medicine if you notice that the vial is damaged or the solution contains particulate matter or appears discoloured.

6. Contents of the pack and other information

What VIZAMYL contains

- The active substance is flutemetamol (^{18}F). Each mL of solution contains flutemetamol (^{18}F) 400 MBq at reference time.
- The other ingredients are sodium chloride and ethanol anhydrous, polysorbate 80, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate and water for injections, see section 2.

What VIZAMYL looks like and contents of the pack

- VIZAMYL is a clear, colourless to slightly yellow solution for injection.
- VIZAMYL is supplied in a 10-mL or 15-mL glass vial. Each vial is stored in a container.
- Not all pack sizes may be marketed.

Marketing Authorisation Holder

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

Manufacturers

Advanced Accelerator Applications S.r.l
Via Piero Maroncelli 40
47014 Meldola (FC)
Italy

Advanced Accelerator Applications
Technopole de l'Aube
14 rue Gustave Eiffel
10430 Rosières près Troyes
France

Seibersdorf Labor GmbH
Grundstück. Nr. 482/2 EZ98 KG
2444 Seibersdorf
Austria

Curium Pharma Spain, S.A.
C/Manuel Bartolome Cossio 10
28040 Madrid
Spain

Curium PET France
Parc scientifique Georges Besse
180 allée Von Neumann
30000 Nîmes
France

Curium Italy S.R.L.
Via Ripamonti 435
20141 Milano (MI)
Italy

Advanced Accelerator Applications Iberica S.L.U
Josep Anselm Clavé 100
Esplugues de Llobregat
Barcelona, 08950
Spain

Advanced Accelerator Applications Ibérica S.L.
Polígono Industrial la Cuesta 3, Parcelas 1 y 2
50100 La Almunia de Doña Godina
Zaragoza
Spain

MAP Medical Technologies Oy
Saukonpaadenranta 2
Helsinki, FI-00180
Finland

Nucleis SA
Allée du Six-Août, 8
4000 Liège
Belgium

Helmholtz-Zentrum Dresden-Rossendorf e.V.
Zentrum für Radiopharmazeutische
Tumorforschung
Bautzner Landstraße 400
01328 Dresden
Germany

ITEL Telecomunicazioni S.r.l.
Via Antonio Labriola Zona Industriale SNC
70037, Ruvo di Puglia (BA)
Italy

This leaflet was last revised in {month YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for medical or healthcare professionals only:

The complete SmPC of VIZAMYL is provided as a separate document in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC {SmPC should be included in the box}.