ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

Excipient(s) 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. The pharmacokinetics of flutemetamol (^{18}F) in patients with renal or hepatic impairment has not been characterised.

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).

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.

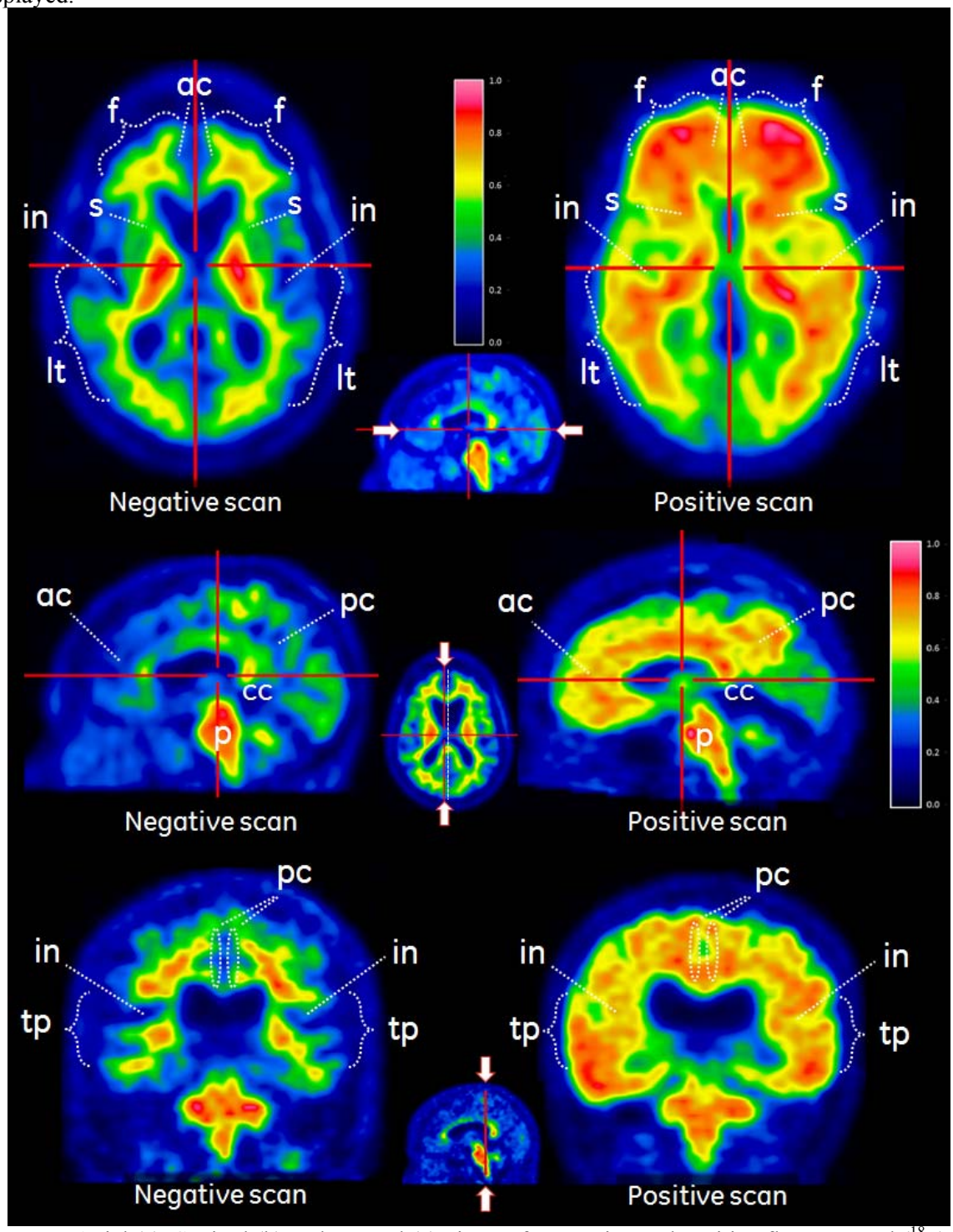

Figure 1. Axial (a), Sagittal (b) and coronal (c) views of a negative and positive flutemetamol (^{18}F) scans (left and right respectively). The negative images show a sulcal/gyral white matter pattern. The sulcal and gyral pattern is not discernible in the positive images on the right. Note that the 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 and **s** striatum. White matter – **p** pons and **cc** corpus callosum.

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 (^{18}F) 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 1.8 mmol (or 41 mg) sodium per dose; 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 (^{18}F) 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 (^{18}F) (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 (^{18}F) 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 761 subjects.

Tabulated list of adverse reactions
The frequencies of adverse reactions are defined as follows:
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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	Dyspepsia Abdominal discomfort Oral discomfort Vomiting
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 (^{18}F) 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 theYellow Card Scheme at www.mhra.gov.uk/yellowcard

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 Abeta.

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 amnestic 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.

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.

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.

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

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, encourage hydration before and after VIZAMYL administration in order to permit frequent voiding. Encourage the patient 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 Limited
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA
United Kingdom

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

10. DATE OF REVISION OF THE TEXT

08/2014

11. DOSIMETRY

Table 2 below shows the dosimetry as calculated using the OLINDA/EXM (**O**rgan **L**evel **IN**ternal **D**ose **A**ssessment/**E**xponential **M**odeling) 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 (^{18}F) 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.