ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amyvid 800 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 800 MBq of florbetapir (^{18}F) at the date and time of calibration (ToC).

The activity per vial ranges from 800 MBq to 12000 MBq at the date and time of calibration.

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:
This medicinal product contains 79 mg/mL of ethanol and up to 37 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Amyvid is a radiopharmaceutical 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. Amyvid 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 florbetapir (^{18}F) should be requested by physicians skilled in the clinical management of neurodegenerative disorders.

Amyvid images should only be interpreted by readers trained in the interpretation of PET images with florbetapir (^{18}F). A recent co-registered computed tomography (CT) scan or magnetic resonance (MR) imaging of the patient to get 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. Image interpretation).

Posology
The recommended activity for an adult weighing 70 kg is 370 MBq florbetapir (^{18}F). The volume of the injection should not be less than 1 mL and not exceed 10 mL.

Special populations

Elderly patients
No dose adjustment is recommended based on age.

Renal and 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.

Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed. The pharmacokinetics of florbetapir (^{18}F) in patients with renal or hepatic impairment have not been characterised.

Paediatric population
There is no relevant use of Amyvid in the paediatric population.

Method of administration
For intravenous use.

For multidose use.

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

The dose is administered by intravenous bolus injection, followed by a flush of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose.

Injection of Amyvid through a short intravenous catheter (approximately 4 cm or less) minimizes the potential for adsorption of the active substance to the catheter.

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

Image acquisition
A 10 minute PET image should be acquired starting approximately 30 to 50 minutes after intravenous injection of Amyvid. Patients should be supine with the head positioned to centre the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2.0 and 3.0 mm.

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

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

Renal impairment and hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. Florbetapir (^{18}F) is excreted primarily 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 Amyvid images

Amyvid images should only be interpreted by readers trained in the interpretation of PET images with florbetapir (^{18}F). A negative scan indicates sparse or no density of cortical β-amyloid plaques. A positive scan indicates moderate to frequent density. Image interpretation errors in the estimation of brain β-amyloid neuritic plaque density, including false negatives, have been observed.

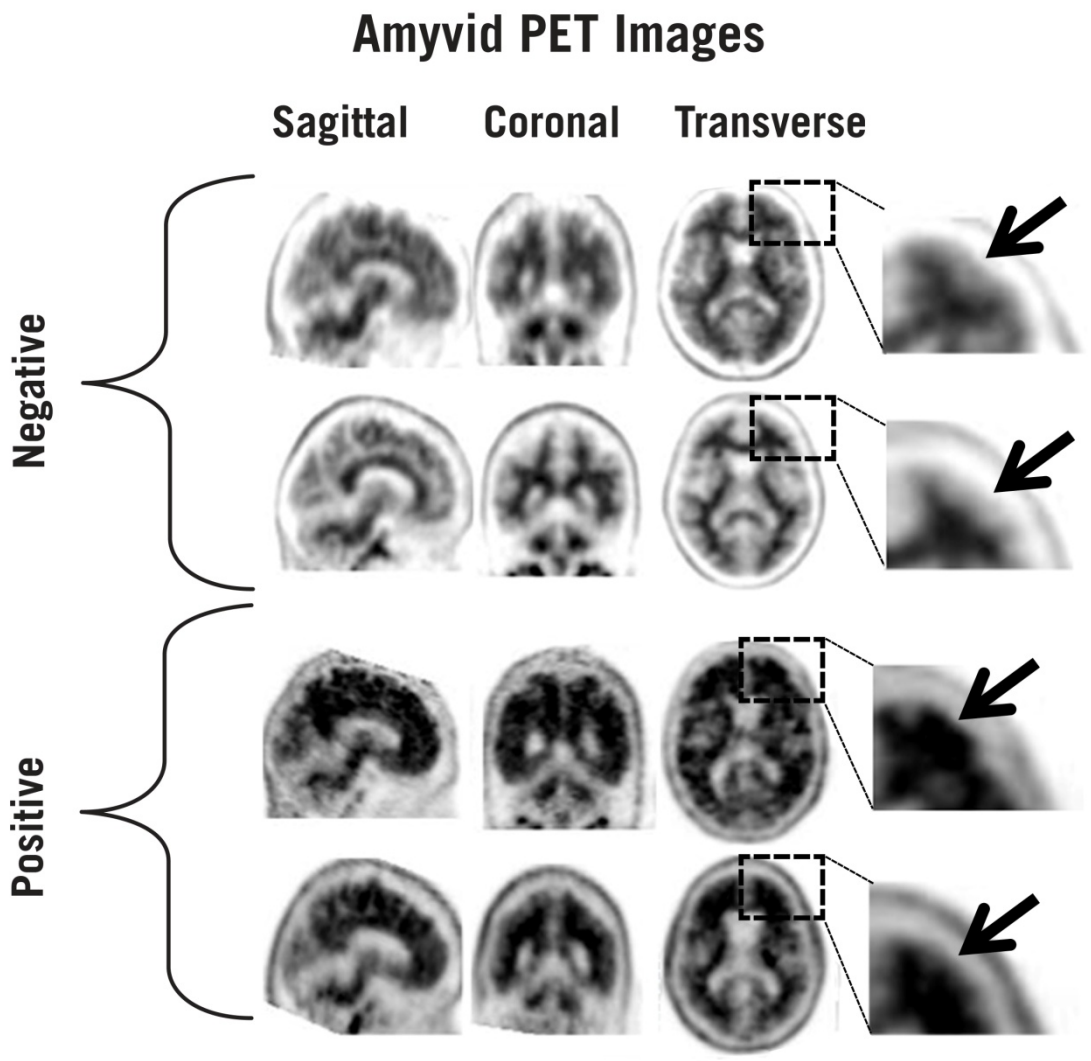
Review of images should be primarily in the transaxial orientation with access as needed to the sagittal and coronal planes. It is recommended that review of images include all transaxial slices of the brain using a black-white scale with the maximum intensity of the scale set to the maximum intensity of all brain pixels.

Interpretation of the image as negative or positive is made by visually comparing the activity in cortical grey matter with activity in adjacent cortical white matter (see Figure 1).

Negative scans have more activity in white matter than in grey matter, creating clear grey-white contrast. Positive scans will have either:

a) Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent grey-white contrast. This is the most common appearance of a positive scan;
b) One or more areas in which grey matter activity is intense and clearly exceeds activity in adjacent white matter.

Figure 1: Amyvid PET cases showing examples of negative scans (top two rows) and positive scans (bottom two rows). Left to right panels show sagittal, coronal, and transverse PET image slices. Final panel to right shows enlarged picture of the brain area in the box. The top two arrows are pointing to normal preserved grey-white contrast with the cortical activity less than the adjacent white matter. The bottom two arrows indicate areas of decreased grey-white contrast with increased cortical activity that is comparable to the activity in the adjacent white matter.



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 and some neurodegenerative dementias (Alzheimer's disease, Lewy body dementia, Parkinson's disease dementia).

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

The efficacy of Amyvid 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.

Increased uptake has been identified in extracerebral structures such as salivary glands, skin, muscles and bone in some cases (see section 5.2). Examination of sagittal images and co-registered CT or MR images could help to distinguish occipital bone from occipital grey matter.

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

Specific warnings
The content of sodium is greater than 1 mmol (up to 37 mg per dose). This should be taken into account in patients on a low sodium diet.

This medicinal product contains 10 vol % ethanol (alcohol), i.e. up to 790 mg per dose, equivalent to 20 mL beer or 8 mL wine per dose.
This amount may be harmful for those suffering from alcoholism, and should be taken into account in pregnant and breast-feeding women and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed.

In vitro binding studies have not shown interference of florbetapir (^{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 very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy
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.
No studies have been conducted in pregnant women. No animal studies have been conducted to investigate the reproductive effects of florbetapir (^{18}F) (see section 5.3).

Breast-feeding
It is not known whether florbetapir (^{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 what is 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

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions have been collected in clinical studies involving 555 subjects and 665 administrations of Amyvid solution for injection. No serious adverse reactions related to Amyvid administration have been reported.

List of adverse reactions
Frequencies are defined as 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); not known (cannot be estimated from the available data). While they may in reality occur at lower frequencies than indicated below, the size of the source database did not allow for the assignment of frequency categories lower than the category "uncommon" (≥1/1,000 to <1/100).

Nervous system disorders
Common: headache
Uncommon: dysgeusia

Vascular disorders
Uncommon: flushing

Gastrointestinal disorders
Uncommon: nausea

Skin and subcutaneous tissue disorders
Uncommon: pruritis, urticaria

General disorders and administration site conditions
Uncommon: infusion site rash

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 7 mSv when the recommended activity of 370 MBq of florbetapir (^{18}F) is administered, these adverse reactions are expected to occur with low probability.

4.9 Overdose

Due to the small quantity of florbetapir (^{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 defaecation. 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: V09AX05

Mechanism of action
Florbetapir (^{18}F) binds to β-amyloid neuritic plaques. Binding studies using traditional neuropathological staining methods in post-mortem AD brains demonstrated statistically significant

($p < 0.0001$) correlations between *in vitro* florbetapir (^{18}F) binding and β-amyloid aggregate deposition. *In vivo*, correlation was assessed in end-of-life patients between florbetapir (^{18}F) uptake in cortical grey matter and the total β-amyloid burden using 4G8 anti-amyloid antibody that stains β-amyloid found in both neuritic and diffuse plaques. The *in vivo* binding of florbetapir (^{18}F) to other β-amyloid structures or other brain structures or receptors remains unknown.

Pharmacodynamic effects

At the low chemical concentrations present in Amyvid, florbetapir (^{18}F) does not have any detectable pharmacological activity.

In completed clinical trials, uptake of florbetapir (^{18}F) in 6 predefined cortical areas of the brain (precuneus, frontal, anterior cingulate, posterior cingulate, parietal and temporal) was measured quantitatively using standardised uptake values (SUV). Cortical average SUV ratios (SUVRs, relative to cerebellum) are higher in AD patients compared with those of healthy volunteer subjects. The average cortical to cerebellar SUVR values in AD patients show continual substantial increases from time zero through 30 minutes post-administration, with only small changes thereafter up to 90 minutes post-injection. No differences in SUVR results were noted in subjects taking common AD treatments relative to those not taking AD treatments.

Clinical efficacy

A pivotal study in 59 end-of-life patients was aimed at establishing the diagnostic performance of Amyvid to detect the cortical neuritic plaque density (no or sparse vs. moderate or frequent). The PET results were compared with the maximal neuritic plaque density measured on sections of frontal, temporal or parietal cortex at the patient's autopsy within 24 months of PET scan. The cognitive status of the subjects could not be reliably measured. In all 59 subjects, a blinded PET reading by 5 nuclear medicine physicians resulted in a majority read sensitivity of 92% (95% CI: 78-98%) and specificity of 100% (95% CI: 80-100%). In a study of 47 young (<40 years) healthy volunteers, presumed to be free of β-amyloid, all Amyvid PET scans were negative.

Sensitivity and specificity to detect the cortical neuritic plaque density of Amyvid was further investigated in two additional studies, in which different sets of readers interpreted images from some subjects followed to autopsy in the pivotal study. Their results closely paralleled the results obtained in the pivotal trial. Inter-rater agreement using Fleiss' kappa values ranged from 0.75 to 0.85.

In a longitudinal study, 142 subjects (clinically diagnosed as MCI, AD or cognitively normal) underwent baseline florbetapir (^{18}F) PET scans, and were followed for 3 years to evaluate the relationship between Amyvid imaging and changes in diagnostic status.

Diagnostic performance values of florbetapir (^{18}F) PET are tabulated below:

	Agreement with baseline diagnosis of MCI N=51	*Agreement with baseline diagnosis of clinical AD* N=31
Sensitivity	19/51 = 37.3% (95% CI: 24.1-51.9%)	21/31 = 67.7% (95% CI: 51.3-84.2%)
Specificity	*Using non-MCI cases (cognitively normal & clinical AD)* 69/100 = 69.0% (95% CI: 59.9-78.1%)	*Using non-AD cases (cognitively normal & MCI)* 91/120 = 75.8% (95% CI: 68.2-83.5%)
Positive likelihood ratio	1.20 (95% CI: 0.76-1.91)	2.80 (95% CI: 1.88-4.18)

Of the patients who had been clinically diagnosed with MCI at study entry, 9 (19%) converted to clinical AD 36 months later. Of the 17 MCI patients who had a positive PET scan, 6 (35%) were diagnosed with clinical probable AD 36 months later compared to 3 (10%) of 30 who had a negative

scan. Sensitivity of Amyvid scan to show the MCI conversion rate to AD in 9 converters was 66.7% (95% CI: 35-88%), specificity in 38 non-converters was 71.0% (95% CI: 55-83%) and positive likelihood ratio was 2.31 (95% CI: 1.2-4.5). 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 Amyvid in all subsets of the paediatric population as there is no intended use in the paediatric population.

5.2 Pharmacokinetic properties

Distribution
Florbetapir (^{18}F) is distributed throughout the body within several minutes of injection, and then is rapidly metabolised.

Organ uptake
Maximal brain uptake of florbetapir (^{18}F) occurs within several minutes of injection, followed by rapid brain clearance during the first 30 minutes following injection. The organs of greatest exposure are organs of elimination, mainly the gallbladder, liver, and intestines.

Healthy controls show relatively low levels of florbetapir (^{18}F) retention in cortex and cerebellum. Regional analyses show slightly higher levels of retention in the caudate, putamen and hippocampus. The highest level of uptake is in regions mainly composed of white matter (pons and centrum semiovale). In AD subjects, cortical regions and putamen show significantly greater uptake compared to controls. In AD subjects, as in controls, there is low retention in cerebellum and hippocampus and high retention in pons and centrum semiovale.

The biophysical basis of the white matter retention of florbetapir (^{18}F) in the living human brain cannot be definitively explained. It is hypothesized that slower clearance of the radiopharmaceutical may contribute to white matter retention since regional cerebral blood flow in white matter is less than half of that of cortex. Uptake has also been identified in some cases in extracerebral structures such as scalp, salivary glands, muscles and cranial bone. The reason for this uptake is unknown, but may be due to accumulation of florbetapir (^{18}F) or to any of its radioactive metabolites or to blood radioactivity.

Elimination
Elimination occurs primarily by clearance through the liver and excretion into the gallbladder and the intestines. Some accumulation/excretion is also observed in the urinary bladder. Radioactivity in urine is present as polar metabolites of florbetapir (^{18}F).

Half-life
Florbetapir (^{18}F) is very rapidly cleared from circulation post-intravenous injection. Less than 5% of the injected ^{18}F radioactivity remains in blood 20 minutes following administration, and less than 2% is present 45 minutes after administration. The residual ^{18}F in circulation during the 30-90 minute imaging window is principally in the form of polar ^{18}F species. The radioactive half-life of ^{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

Animal toxicology and safety pharmacology
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single and repeated dose toxicity, in which florbetapir [the non-radioactive form of florbetapir (^{18}F)] was used. An acute dose study was conducted in rats, and the NOAEL (no

observable adverse effect level) was determined to be at least 100 times maximum human dose. The potential toxicity of 28 days of repeated intravenous injections of florbetapir was tested in rats and dogs, and the NOAEL was found to be at least 25 times the maximum human dose.

In an *in vitro* bacterial reverse mutation assay (Ames test), increases in the number of revertant colonies were observed in 2 of the 5 strains exposed to florbetapir. In a chromosomal aberration *in vitro* study with cultured human peripheral lymphocyte cells, florbetapir did not increase the percent of cells with structural aberrations with 3 hour exposure with or without activation; however, 22 hour exposure produced an increase in structural aberrations at all tested concentrations. Potential *in vivo* genotoxicity of florbetapir was evaluated in a rat micronucleus study. In this assay, florbetapir did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level, 372 µg/kg/day, when given twice daily for 3 consecutive days. This dose is approximately 500 times the maximum human dose, and showed no evidence of mutagenicity.

No studies have been conducted in animals to investigate the potential long term carcinogenicity, fertility, or reproductive effects of florbetapir (^{18}F).

No animal toxicology and safety pharmacology studies have been performed with florbetapir (^{18}F).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, absolute
Sodium ascorbate
Sodium chloride
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

7.5 hours from the time of calibration

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

For the storage precautions after first opening, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Amyvid is supplied in 10 mL or 15 mL clear Type I borosilicate glass vials with FluroTec-coated chlorobutyl elastomeric stoppers and aluminium seals.

One multidose vial of 10 mL capacity contains 1 to 10 mL of solution, corresponding to 800 to 8000 MBq at date and time of calibration.
One multidose vial of 15 mL capacity contains 1 to 15 mL of solution, corresponding to 800 to 12000 MBq at date and time of calibration.

As a result of differences in the manufacturing process, it is possible that vials of some product batches are distributed with punctured rubber stoppers.

Each vial is enclosed in a shielded container of appropriate thickness to minimise external radiation exposure.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

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 which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

If 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 (including pregnant healthcare professionals) from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7 MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY

The estimated absorbed radiation doses to organs and tissues of an average adult patient (70 kg) per 370 MBq of florbetapir (^{18}F) using standard methods for dosimetry calculations (ICRP Volume 30) is tabulated below. No assumptions were made regarding urinary bladder voiding.

Organ/tissue	Dose absorbed per activity administered (µGy/MBq) Average
Adrenal	13.6
Brain	10.0
Breasts	6.2
Gallbladder wall	143.0
Lower large intestine wall	27.8
Small intestine	65.5
Stomach wall	11.7
Upper large intestine wall	74.4
Heart wall	12.7
Kidneys	13.0
Liver	64.4
Lungs	8.5
Muscle	8.6
Ovaries	17.6
Pancreas	14.4
Red marrow	14.3
Osteogenic cells	27.6
Skin	5.9
Spleen	8.9
Testes	6.8
Thymus	7.3
Thyroid	6.8
Urinary bladder wall	27.1
Uterus	15.6
Total body	11.6
Effective Dose *[µSv/MBq]*[a]	**18.6**

[a] Assumed quality factor (Q) of 1 for conversion of absorbed dose to effective dose for ^{18}F.

The effective dose resulting from the administration of a 370 MBq dose for an adult weighing 70 kg is about 7 mSv. 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 370 MBq the typical radiation dose to the target organ (brain) is 3.7 mGy.

For an administered activity of 370 MBq the typical radiation doses delivered to the critical organs, gallbladder, upper large intestine wall, lower large intestine wall, small intestine and liver are 53 mGy, 27.5 mGy, 10.3 mGy, 24.2 mGy and 23.8 mGy, respectively.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation
The package must be checked before use and the activity measured using an activimeter.

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

Amyvid may be diluted aseptically with sodium chloride 9 mg/mL (0.9%) solution for injection to a maximum dilution of 1:5. Diluted product must be used within 4 hours of dilution.

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

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

1. NAME OF THE MEDICINAL PRODUCT

Amyvid 1900 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 1900 MBq of florbetapir (^{18}F) at the date and time of calibration (ToC).

The activity per vial ranges from 1900 MBq to 28500 MBq at the date and time of calibration.

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:
This medicinal product contains 79 mg/mL of ethanol and up to 37 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Amyvid is a radiopharmaceutical 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. Amyvid 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 florbetapir (^{18}F) should be requested by physicians skilled in the clinical management of neurodegenerative disorders.

Amyvid images should only be interpreted by readers trained in the interpretation of PET images with florbetapir (^{18}F). A recent co-registered computed tomography (CT) scan or magnetic resonance (MR) imaging of the patient to get 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. Image interpretation).

Posology
The recommended activity for an adult weighing 70 kg is 370 MBq florbetapir (^{18}F). The volume of the injection should not be less than 1 mL and not exceed 10 mL.

Special populations

Elderly patients
No dose adjustment is recommended based on age.

Renal and 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.

Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed. The pharmacokinetics of florbetapir (^{18}F) in patients with renal or hepatic impairment have not been characterised.

Paediatric population
There is no relevant use of Amyvid in the paediatric population.

Method of administration
For intravenous use.

For multidose use.

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

The dose is administered by intravenous bolus injection, followed by a flush of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose.

Injection of Amyvid through a short intravenous catheter (approximately 4 cm or less) minimizes the potential for adsorption of the active substance to the catheter.

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

Image acquisition
A 10 minute PET image should be acquired starting approximately 30 to 50 minutes after intravenous injection of Amyvid. Patients should be supine with the head positioned to centre the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2.0 and 3.0 mm.

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

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

Renal impairment and hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. Florbetapir (^{18}F) is excreted primarily 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 Amyvid images

Amyvid images should only be interpreted by readers trained in the interpretation of PET images with florbetapir (^{18}F). A negative scan indicates sparse or no density of cortical β-amyloid plaques. A positive scan indicates moderate to frequent density. Image interpretation errors in the estimation of brain β-amyloid neuritic plaque density, including false negatives, have been observed.

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Negative scans have more activity in white matter than in grey matter, creating clear grey-white contrast. Positive scans will have either:

a) Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent grey-white contrast. This is the most common appearance of a positive scan;
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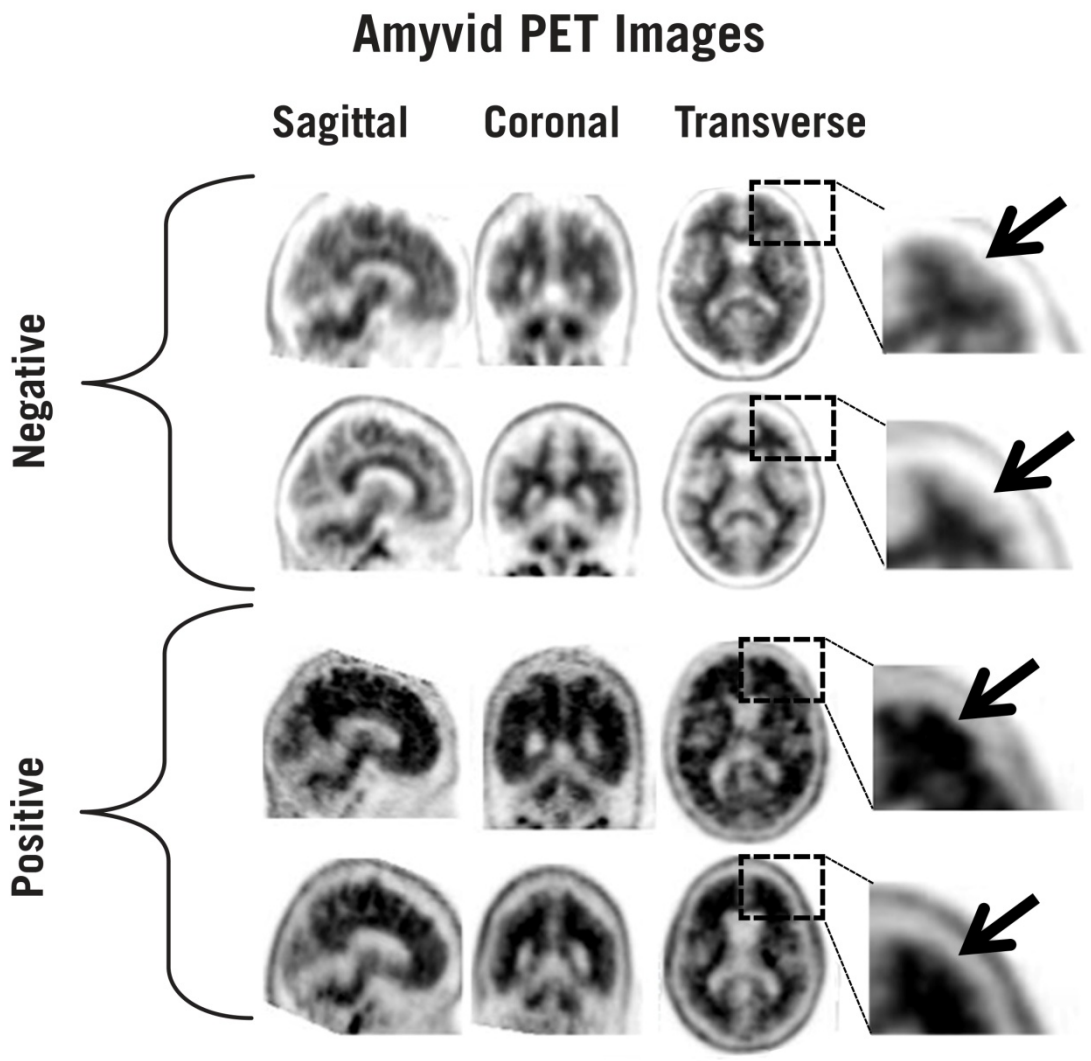

Limitations of use

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 and some neurodegenerative dementias (Alzheimer's disease, Lewy body dementia, Parkinson's disease dementia).

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

The efficacy of Amyvid 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.

Increased uptake has been identified in extracerebral structures such as salivary glands, skin, muscles and bone in some cases (see section 5.2). Examination of sagittal images and co-registered CT or MR images could help to distinguish occipital bone from occipital grey matter.

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

Specific warnings
The content of sodium is greater than 1 mmol (up to 37 mg per dose). This should be taken into account in patients on a low sodium diet.

This medicinal product contains 10 vol % ethanol (alcohol), i.e. up to 790 mg per dose, equivalent to 20 mL beer or 8 mL wine per dose.
This amount may be harmful for those suffering from alcoholism, and should be taken into account in pregnant and breast-feeding women and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed.

In vitro binding studies have not shown interference of florbetapir (^{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 very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy
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.
No studies have been conducted in pregnant women. No animal studies have been conducted to investigate the reproductive effects of florbetapir (^{18}F) (see section 5.3).

Breast-feeding
It is not known whether florbetapir (^{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 what is 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

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions have been collected in clinical studies involving 555 subjects and 665 administrations of Amyvid solution for injection. No serious adverse reactions related to Amyvid administration have been reported.

List of adverse reactions
Frequencies are defined as 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); not known (cannot be estimated from the available data). While they may in reality occur at lower frequencies than indicated below, the size of the source database did not allow for the assignment of frequency categories lower than the category "uncommon" (≥1/1,000 to <1/100).

Nervous system disorders
Common: headache
Uncommon: dysgeusia

Vascular disorders
Uncommon: flushing

Gastrointestinal disorders
Uncommon: nausea

Skin and subcutaneous tissue disorders
Uncommon: pruritis, urticaria

General disorders and administration site conditions
Uncommon: infusion site rash

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 7 mSv when the recommended activity of 370 MBq of florbetapir (^{18}F) is administered, these adverse reactions are expected to occur with low probability.

4.9 Overdose

Due to the small quantity of florbetapir (^{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 defaecation. 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: V09AX05

Mechanism of action
Florbetapir (^{18}F) binds to β-amyloid neuritic plaques. Binding studies using traditional neuropathological staining methods in post-mortem AD brains demonstrated statistically significant

($p < 0.0001$) correlations between *in vitro* florbetapir (^{18}F) binding and β-amyloid aggregate deposition. *In vivo*, correlation was assessed in end-of-life patients between florbetapir (^{18}F) uptake in cortical grey matter and the total β-amyloid burden using 4G8 anti-amyloid antibody that stains β-amyloid found in both neuritic and diffuse plaques. The *in vivo* binding of florbetapir (^{18}F) to other β-amyloid structures or other brain structures or receptors remains unknown.

Pharmacodynamic effects

At the low chemical concentrations present in Amyvid, florbetapir (^{18}F) does not have any detectable pharmacological activity.

In completed clinical trials, uptake of florbetapir (^{18}F) in 6 predefined cortical areas of the brain (precuneus, frontal, anterior cingulate, posterior cingulate, parietal and temporal) was measured quantitatively using standardised uptake values (SUV). Cortical average SUV ratios (SUVRs, relative to cerebellum) are higher in AD patients compared with those of healthy volunteer subjects. The average cortical to cerebellar SUVR values in AD patients show continual substantial increases from time zero through 30 minutes post-administration, with only small changes thereafter up to 90 minutes post-injection. No differences in SUVR results were noted in subjects taking common AD treatments relative to those not taking AD treatments.

Clinical efficacy

A pivotal study in 59 end-of-life patients was aimed at establishing the diagnostic performance of Amyvid to detect the cortical neuritic plaque density (no or sparse vs. moderate or frequent). The PET results were compared with the maximal neuritic plaque density measured on sections of frontal, temporal or parietal cortex at the patient's autopsy within 24 months of PET scan. The cognitive status of the subjects could not be reliably measured. In all 59 subjects, a blinded PET reading by 5 nuclear medicine physicians resulted in a majority read sensitivity of 92% (95% CI: 78-98%) and specificity of 100% (95% CI: 80-100%). In a study of 47 young (<40 years) healthy volunteers, presumed to be free of β-amyloid, all Amyvid PET scans were negative.

Sensitivity and specificity to detect the cortical neuritic plaque density of Amyvid was further investigated in two additional studies, in which different sets of readers interpreted images from some subjects followed to autopsy in the pivotal study. Their results closely paralleled the results obtained in the pivotal trial. Inter-rater agreement using Fleiss' kappa values ranged from 0.75 to 0.85.

In a longitudinal study, 142 subjects (clinically diagnosed as MCI, AD or cognitively normal) underwent baseline florbetapir (^{18}F) PET scans, and were followed for 3 years to evaluate the relationship between Amyvid imaging and changes in diagnostic status.

Diagnostic performance values of florbetapir (^{18}F) PET are tabulated below:

	Agreement with baseline diagnosis of MCI N=51	*Agreement with baseline diagnosis of clinical AD* N=31
Sensitivity	19/51 = 37.3% (95% CI: 24.1-51.9%)	21/31 = 67.7% (95% CI: 51.3-84.2%)
Specificity	*Using non-MCI cases (cognitively normal & clinical AD)* 69/100 = 69.0% (95% CI: 59.9-78.1%)	*Using non-AD cases (cognitively normal & MCI)* 91/120 = 75.8% (95% CI: 68.2-83.5%)
Positive likelihood ratio	1.20 (95% CI: 0.76-1.91)	2.80 (95% CI: 1.88-4.18)

Of the patients who had been clinically diagnosed with MCI at study entry, 9 (19%) converted to clinical AD 36 months later. Of the 17 MCI patients who had a positive PET scan, 6 (35%) were diagnosed with clinical probable AD 36 months later compared to 3 (10%) of 30 who had a negative

scan. Sensitivity of Amyvid scan to show the MCI conversion rate to AD in 9 converters was 66.7% (95% CI: 35-88%), specificity in 38 non-converters was 71.0% (95% CI: 55-83%) and positive likelihood ratio was 2.31 (95% CI: 1.2-4.5). 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 Amyvid in all subsets of the paediatric population as there is no intended use in the paediatric population.

5.2 Pharmacokinetic properties

Distribution
Florbetapir (^{18}F) is distributed throughout the body within several minutes of injection, and then is rapidly metabolised.

Organ uptake
Maximal brain uptake of florbetapir (^{18}F) occurs within several minutes of injection, followed by rapid brain clearance during the first 30 minutes following injection. The organs of greatest exposure are organs of elimination, mainly the gallbladder, liver, and intestines.

Healthy controls show relatively low levels of florbetapir (^{18}F) retention in cortex and cerebellum. Regional analyses show slightly higher levels of retention in the caudate, putamen and hippocampus. The highest level of uptake is in regions mainly composed of white matter (pons and centrum semiovale). In AD subjects, cortical regions and putamen show significantly greater uptake compared to controls. In AD subjects, as in controls, there is low retention in cerebellum and hippocampus and high retention in pons and centrum semiovale.

The biophysical basis of the white matter retention of florbetapir (^{18}F) in the living human brain cannot be definitively explained. It is hypothesized that slower clearance of the radiopharmaceutical may contribute to white matter retention since regional cerebral blood flow in white matter is less than half of that of cortex. Uptake has also been identified in some cases in extracerebral structures such as scalp, salivary glands, muscles and cranial bone. The reason for this uptake is unknown, but may be due to accumulation of florbetapir (^{18}F) or to any of its radioactive metabolites or to blood radioactivity.

Elimination
Elimination occurs primarily by clearance through the liver and excretion into the gallbladder and the intestines. Some accumulation/excretion is also observed in the urinary bladder. Radioactivity in urine is present as polar metabolites of florbetapir (^{18}F).

Half-life
Florbetapir (^{18}F) is very rapidly cleared from circulation post-intravenous injection. Less than 5% of the injected ^{18}F radioactivity remains in blood 20 minutes following administration, and less than 2% is present 45 minutes after administration. The residual ^{18}F in circulation during the 30-90 minute imaging window is principally in the form of polar ^{18}F species. The radioactive half-life of ^{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

Animal toxicology and safety pharmacology
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single and repeated dose toxicity, in which florbetapir [the non-radioactive form of florbetapir (^{18}F)] was used. An acute dose study was conducted in rats, and the NOAEL (no

observable adverse effect level) was determined to be at least 100 times maximum human dose. The potential toxicity of 28 days of repeated intravenous injections of florbetapir was tested in rats and dogs, and the NOAEL was found to be at least 25 times the maximum human dose.

In an *in vitro* bacterial reverse mutation assay (Ames test), increases in the number of revertant colonies were observed in 2 of the 5 strains exposed to florbetapir. In a chromosomal aberration *in vitro* study with cultured human peripheral lymphocyte cells, florbetapir did not increase the percent of cells with structural aberrations with 3 hour exposure with or without activation; however, 22 hour exposure produced an increase in structural aberrations at all tested concentrations. Potential *in vivo* genotoxicity of florbetapir was evaluated in a rat micronucleus study. In this assay, florbetapir did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level, 372 µg/kg/day, when given twice daily for 3 consecutive days. This dose is approximately 500 times the maximum human dose, and showed no evidence of mutagenicity.

No studies have been conducted in animals to investigate the potential long term carcinogenicity, fertility, or reproductive effects of florbetapir (^{18}F).

No animal toxicology and safety pharmacology studies have been performed with florbetapir (^{18}F).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, absolute
Sodium ascorbate
Sodium chloride
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

10 hours from the time of calibration.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

For the storage precautions after first opening, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Amyvid is supplied in 10 mL or 15 mL clear Type I borosilicate glass vials with FluroTec-coated chlorobutyl elastomeric stoppers and aluminium seals.

One multidose vial of 10 mL capacity contains 1 to 10 mL of solution, corresponding to 1900 to 19000 MBq at date and time of calibration.
One multidose vial of 15 mL capacity contains 1 to 15 mL of solution, corresponding to 1900 to 28500 MBq at date and time of calibration.

As a result of differences in the manufacturing process, it is possible that vials of some product batches are distributed with punctured rubber stoppers.

Each vial is enclosed in a shielded container of appropriate thickness to minimise external radiation exposure.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

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 which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

If 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 (including pregnant healthcare professionals) from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7 MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY

The estimated absorbed radiation doses to organs and tissues of an average adult patient (70 kg) per 370 MBq of florbetapir (^{18}F) using standard methods for dosimetry calculations (ICRP Volume 30) is tabulated below. No assumptions were made regarding urinary bladder voiding.

Organ/tissue	Dose absorbed per activity administered (µGy/MBq) Average
Adrenal	13.6
Brain	10.0
Breasts	6.2
Gallbladder wall	143.0
Lower large intestine wall	27.8
Small intestine	65.5
Stomach wall	11.7
Upper large intestine wall	74.4
Heart wall	12.7
Kidneys	13.0
Liver	64.4
Lungs	8.5
Muscle	8.6
Ovaries	17.6
Pancreas	14.4
Red marrow	14.3
Osteogenic cells	27.6
Skin	5.9
Spleen	8.9
Testes	6.8
Thymus	7.3
Thyroid	6.8
Urinary bladder wall	27.1
Uterus	15.6
Total body	11.6
Effective Dose *[µSv/MBq]*[a]	**18.6**

[a] Assumed quality factor (Q) of 1 for conversion of absorbed dose to effective dose for ^{18}F.

The effective dose resulting from the administration of a 370 MBq dose for an adult weighing 70 kg is about 7 mSv. 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 370 MBq the typical radiation dose to the target organ (brain) is 3.7 mGy.

For an administered activity of 370 MBq the typical radiation doses delivered to the critical organs, gallbladder, upper large intestine wall, lower large intestine wall, small intestine and liver are 53 mGy, 27.5 mGy, 10.3 mGy, 24.2 mGy and 23.8 mGy, respectively.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation
The package must be checked before use and the activity measured using an activimeter.

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

Amyvid may be diluted aseptically with sodium chloride 9 mg/mL (0.9%) solution for injection to a maximum dilution of 1:5. Diluted product must be used within 4 hours of dilution.

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

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Advanced Accelerator Applications-Bethune
126 Rocade Sud
62660 Beuvry
France

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

Advanced Accelerator Applications-Saint Genis-Poully
20 Rue Diesel
01630 Saint Genis-Poully
France

Advanced Accelerator Applications Iberica
Avda Navarra 3-5 Pol. Ind. La Cuesta, Sector 3
50100 La Almunia de Dona Godina
Zaragoza
Spain

Cyclopharma Laboratories – Glisy
Allee Nautilus
80440 Glisy
France

Cyclopharma Laboratories – Toulouse Canceropole
Voie interne
31000 Toulouse-Langlade
France

PETNET solutions
Heathfield Way, Nottingham City Hospital, Gate 1
Hucknall Road
Nottingham
NG51PB United Kingdom

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 (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan and the Risk minimisation Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

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 Amyvid is marketed, at launch and after launch, all physicians who are expected to use Amyvid have access to a training course in order to ensure accurate and reliable interpretation of the PET images.

The physician training course should contain the following key elements:

- Information on amyloid pathology in Alzheimer Disease; relevant information on Amyvid as an β-amyloid PET tracer, including the approved indication according to the SmPC, limitations of Amyvid use, interpretation errors, safety information and the results of clinical trials informing on the diagnostic use of Amyvid
- 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 Amyvid PET demonstration cases with correct PET scan interpretation by an experienced reader; Amyvid-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

1. NAME OF THE MEDICINAL PRODUCT

Amyvid 800 MBq/mL solution for injection
Florbetapir (^{18}F)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution for injection contains 800 MBq of florbetapir (^{18}F) at date and time of calibration (ToC).

3. LIST OF EXCIPIENTS

Ethanol, sodium ascorbate, sodium chloride, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial contains
Volume: {Z} mL
Activity: {Y} MBq in {Z}mL at {hh:mm}{Time Zone} on {DD/MM/YYYY}

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intravenous use
Multidose

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 material

8. EXPIRY DATE

EXP{hh:mm}{Time Zone} on{DD/MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

Any unused material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Amyvid 800 MBq/mL solution for injection
Florbetapir (^{18}F)

2. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

3. EXPIRY DATE

EXP: ToC + 7.5 h

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Not more than 12000 MBq at ToC (see outer packaging)

6. OTHER

 Radioactive material

Advanced Accelerator Applications, 62660, Beuvry, France

Advanced Accelerator Applications, 47014, Meldola, Italy

Advanced Accelerator Applications, 01630, Saint Genis Pouilly, France

Advanced Accelerator Applications, 50100, Zaragoza, Spain

Laboratories Cyclopharma, 80440, Glisy, France

Laboratories Cyclopharma, 31000, Toulouse, France

PETNET Solutions, Nottingham, NG5 1PB, United Kingdom

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SHIELD LABEL

1. NAME OF THE MEDICINAL PRODUCT

Amyvid 1900 MBq/mL solution for injection
Florbetapir (^{18}F)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution for injection contains 1900 MBq of florbetapir (^{18}F) at date and time of calibration (ToC).

3. LIST OF EXCIPIENTS

Ethanol, sodium ascorbate, sodium chloride, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial contains
Volume: {Z} mL
Activity: {Y} MBq in {Z}mL at {hh:mm}{Time Zone} on {DD/MM/YYYY}

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intravenous use
Multidose

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 material

8. EXPIRY DATE

EXP{hh:mm}{Time Zone} on{DD/MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

Any unused material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Amyvid 1900 MBq/mL solution for injection
Florbetapir (^{18}F)

2. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

3. EXPIRY DATE

EXP: ToC + 10 h

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Not more than 28500 MBq at ToC (see outer packaging)

6. OTHER

 Radioactive material

Advanced Accelerator Applications, 62660, Beuvry, France

Advanced Accelerator Applications, 47014, Meldola, Italy

Advanced Accelerator Applications, 01630, Saint Genis Pouilly, France

Advanced Accelerator Applications, 50100, Zaragoza, Spain

Laboratories Cyclopharma, 80440, Glisy, France

Laboratories Cyclopharma, 31000, Toulouse, France

PETNET Solutions, Nottingham, NG5 1PB, United Kingdom

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Amyvid 1900 MBq/mL solution for injection
Amyvid 800 MBq/mL solution for injection
Florbetapir (^{18}F)

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 the procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Amyvid is and what it is used for

This medicine is a radiopharmaceutical product for diagnostic use only.

Amyvid contains the active substance florbetapir (^{18}F).

Amyvid is given to people with memory problems so that doctors can perform a type of brain scan, called a PET scan. An Amyvid PET scan, along with other brain function tests, can help your doctor determine whether or not you may have β-amyloid plaques in your brain. This medicine is intended for adults only.
You should discuss the results of the test with the doctor that requested the scan.

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

2. What you need to know before Amyvid is used

Amyvid must not be used
- if you are allergic to florbetapir (^{18}F) 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 Amyvid if you:
- have kidney problems
- have liver problems
- are pregnant or think you may be pregnant
- are breast-feeding

Children and adolescents
Amyvid is not intended for use in children and adolescents.

Other medicines and Amyvid
Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines since they may interfere with the interpretation of the images.

Pregnancy and breast-feeding
You must inform the nuclear medicine doctor before you are given Amyvid 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 your 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 and the maternal milk pumped must be discarded. Resuming breast-feeding should be in agreement with the nuclear medicine doctor who will supervise the procedure.

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
It is considered unlikely that Amyvid will affect your ability to drive or to use machines.

Amyvid contains ethanol and sodium
This medicine contains 10 vol% ethanol (alcohol), i.e. up to 790 mg per dose, equivalent to 20 mL beer or 8 mL wine. This may be harmful to those suffering from alcoholism. It should be taken into account in pregnant or breast-feeding women and high-risk groups such as patients with liver disease or epilepsy.

This medicine also contains sodium ascorbate and sodium chloride. The content of sodium is greater than 1 mmol (up to 37 mg per dose). This should be taken into account in patients with a low sodium diet.

3. How Amyvid will be used

There are strict laws on the use, handling and disposal of radiopharmaceutical products.
Amyvid will only be used in specially controlled areas. This medicine will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this medicine and will keep you informed of their actions.

Dose
The nuclear medicine doctor supervising the procedure will decide on the quantity of Amyvid to be used in your case. It will be the smallest quantity necessary to get the desired information.

The usual amount recommended for an adult is 370 MBq. Megabecquerel (MBq) is the unit used to express radioactivity.

Administration of Amyvid and conduct of the procedure
Amyvid 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 usually sufficient to carry out the scan that your doctor needs.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure. A brain scan is usually taken about 30 to 50 minutes after the Amyvid injection is given.

After administration of Amyvid, you should:
Avoid any close contact with young children and pregnant women for the 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 been given more Amyvid than you should
An overdose is unlikely because you will only receive a single dose of Amyvid precisely controlled by the nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. In particular, the nuclear medicine doctor in charge of the procedure may provide ways to increase the passing of urine and stools in order to help remove radioactivity from your body.

If you have any further question on the use of Amyvid, 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 effect of Amyvid is **common** (may affect up to 1 in 10 people):
- headache

The following side effects of Amyvid are **uncommon** (may affect up to 1 in 100 people).
- feeling sick,
- altered taste,
- flushing,
- itching,
- rash where the injection is given or in other places.

This radiopharmaceutical will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities (i.e. genetic diseases). See also section 1.

If you get any side effects talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet.

5. How Amyvid 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.
Amyvid must not be used after the expiry date which is stated on the shield label after EXP.

6. Contents of the pack and other information

What Amyvid Contains
- The active substance is florbetapir (^{18}F).

Amyvid 1900 MBq/mL: 1 mL of solution for injection contains 1900 MBq of florbetapir (^{18}F) at the date and time of calibration.
Amyvid 800 MBq/mL: 1 mL of solution for injection contains 800 MBq of florbetapir (^{18}F) at the date and time of calibration.

- The other ingredients are ethanol, sodium ascorbate, sodium chloride, water for injections (see section 2 Amyvid contains ethanol and sodium).

What Amyvid looks like and contents of the pack
Amyvid is a clear, colourless solution for injection. It is supplied in a 10 mL or 15 mL clear Type I borosilicate glass vial.

Pack size:
Amyvid 1900 MBq/mL: One multidose vial of 10 mL capacity containing 1 to 10 mL of solution, corresponding to 1900 to 19000 MBq at date and time of calibration.
One multidose vial of 15 mL capacity containing 1 to 15 mL of solution, corresponding to 1900 to 28.500 MBq at date and time of calibration.
Amyvid 800 MBq/mL: One multidose vial of 10 mL capacity containing 1 to 10 mL of solution, corresponding to 800 to 8000 MBq at date and time of calibration.
One multidose vial of 15 mL capacity containing 1 to 15 mL of solution, corresponding to 800 to 12000 MBq at date and time of calibration.

Marketing Authorisation Holder and Manufacturer

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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 Amyvid 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}.