

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amyvid 800 MBq/mL solution for injection
Amyvid 1,900 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amyvid 800 MBq/mL solution for injection

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 12,000 MBq at the ToC.

Amyvid 1,900 MBq/mL solution for injection

Each mL of solution for injection contains 1,900 MBq of florbetapir (^{18}F) at the ToC.

The activity per vial ranges from 1,900 MBq to 28,500 MBq at the ToC.

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

Excipients with known effect

Each dose contains up to 790 mg of ethanol and 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

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

Amyvid is for intravenous use and 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 florbetapir (^{18}F) through a short intravenous catheter (approximately 4 cm or less) minimises 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

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.

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.

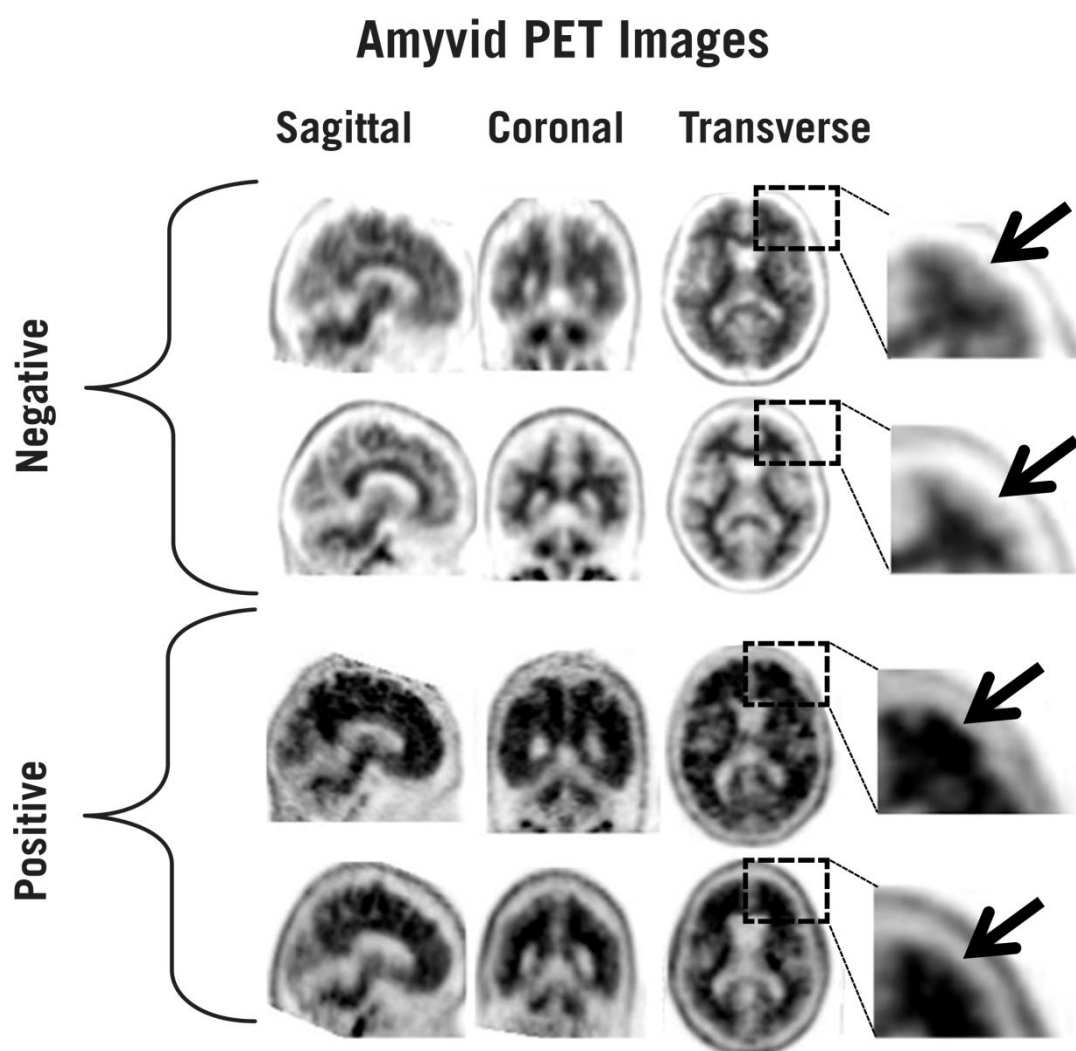
Review of images should be primarily in the transaxial orientation with access as needed to the sagittal and coronal planes. It is recommended that review of images include all transaxial slices of the brain using a black-white scale with the maximum intensity of the scale set to the maximum intensity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

- 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; or
- 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.



Adjunctive use of quantitative information for image interpretation:

Adjunctive use of amyloid PET quantitative information should only be used by readers trained in the application of quantitative information to aid visual image interpretation, including recommendations for selection of appropriate software to support the methods. Incorporation of quantitative information generated by CE-marked image quantitation software as an adjunct to the visual interpretation method may improve readers' accuracy. Readers should visually interpret the scan, then perform quantitation according to manufacturer's instructions, including quality checks of the quantitative process, and

compare quantitation of scan with typical ranges for negative and positive scans. If the quantitation result is inconsistent with the initial visual interpretation:

1. The spatial normalisation and fit of the scan to the template should be re-checked to confirm the accuracy of the placement of the regions of interest (ROIs), search for CSF or bone within the ROI, and evaluate the potential impact of atrophy or ventriculomegaly on quantitation.
2. The basis for making a visual positive or negative determination should be reviewed:
 - a. In the case of an amyloid positive initial visual read and negative quantitation, the physician should consider whether the positive visual interpretation might be based on tracer retention in regions outside the ROIs that contribute to the cortical average standardised uptake value ratio (SUVR).
 - b. In the case of an amyloid negative initial visual read and an amyloid positive quantitation, the regions corresponding to the ROIs with elevated SUVR should be examined to determine whether there is a loss of grey/white contrast in these areas.
3. The cerebellum region should be examined to confirm the fit of the ROI and the level of grey/white contrast, which provides a standard for visual comparison to cortex. Possible structural anomalies that could influence quantitation of the cerebellar region should be considered.
4. A final interpretation of the scan should be made based on the final visual read after conducting resolution steps 1-3 above.

After the procedure

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

Sodium

This medicinal product contains up to 37 mg sodium per dose, equivalent to 1.85 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Ethanol

This medicinal product contains 790 mg of alcohol (ethanol) in each 10 mL dose, which is equivalent to 11.3 mg/kg (administered to an adult with 70 kg). The amount in 10 mL of this medicinal product is equivalent to less than 20 mL beer or 8 mL wine.

The small amount of alcohol in this medicinal product will not have any noticeable effects.

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 (¹⁸F) binding to β -amyloid plaques in the presence of other common medicinal products taken by AD patients.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is 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

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Amyvid is based on its administrations to 2,105 subjects in clinical trials.

Tabulated list of adverse reactions

Frequencies are defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); 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” ($\geq 1/1,000$ to $< 1/100$).

System organ class	Common	Uncommon
Nervous system disorders	Headache	Dysgeusia
Vascular disorders		Flushing
Gastrointestinal disorders		Nausea
Skin and subcutaneous tissue disorders		Pruritus Urticaria
General disorders and administration site conditions		Injection site reaction ^a Infusion site rash

^aInjection site reaction includes injection site haemorrhage, injection site irritation, and injection site pain

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.

Reporting of suspected adverse reactions

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

4.9 Overdose

Due to the small quantity of 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:

	<i>Agreement with baseline diagnosis of MCI</i> N=51	<i>Agreement with baseline diagnosis of clinical AD</i> N=31
Sensitivity	19/51 = 37.3% (95% CI: 24.1-51.9%)	21/31 = 67.7% (95% CI: 51.3-84.2%)
Specificity	<i>Using non-MCI cases (cognitively normal & clinical AD)</i> 69/100 = 69.0% (95% CI: 59.9-78.1%)	<i>Using non-AD cases (cognitively normal & MCI)</i> 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.

Adjunctive use of quantitative information for image interpretation

The feasibility and reliability of using CE-marked quantitative software as an adjunct to clinical qualitative interpretation was investigated in two studies using three different commercially available quantitative software packages. Participating readers first evaluated a set of 96 PET scans, including 46 scans with autopsy standard of truth, using the visual qualitative read method to establish a baseline and were subsequently asked to re-evaluate the same set of scans with or without access to quantitative software information. Across all participating readers who had access to quantitative information, average reader accuracy on the scans with autopsy standard of truth improved from 90.1% at baseline to 93.1% (p-value <0.0001), with no observed decrease in either sensitivity or specificity.

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 hypothesised 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 (¹⁸F).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous
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

Amyvid 800 MBq/mL solution for injection

7.5 hours from the ToC

Amyvid 1,900 MBq/mL solution for injection

10 hours from the ToC.

6.4 Special precautions for storage

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

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.

Amyvid 800 MBq/mL solution for injection

One multidose vial of 10 mL capacity contains 1 to 10 mL of solution, corresponding to 800 to 8,000 MBq at ToC.

One multidose vial of 15 mL capacity contains 1 to 15 mL of solution, corresponding to 800 to 12,000 MBq at ToC.

Amyvid 1,900 MBq/mL solution for injection

One multidose vial of 10 mL capacity contains 1 to 10 mL of solution, corresponding to 1,900 to 19,000 MBq at ToC.

One multidose vial of 15 mL capacity contains 1 to 15 mL of solution, corresponding to 1,900 to 28,500 MBq at ToC.

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.
Papendorpseweg 83
3528 BJ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/805/001
EU/1/12/805/002
EU/1/12/805/003
EU/1/12/805/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 January 2013

Date of latest renewal: 21 September 2017

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 ($\mu\text{Gy}/\text{MBq}$)
	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 [$\mu\text{Sv}/\text{MBq}$]^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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Advanced Accelerator Applications Germany GmbH
Saime-Genc-Ring 18
53121 Bonn
Germany

PETNET Solutions SAS
ZAC du Bois Chaland
15 rue des Pyrénées
91090 Lisses
France

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

• Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

• Additional risk minimisation measures

Prior to launch in each Member State the 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

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
Volume: {Z} mL
Activity: {Y} MBq in {Z} mL
ToC: {DD/MM/YYYY} {hh:mm} {Time Zone}
Vial No.

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

Advanced Accelerator Applications, 53121, Bonn, Germany

PETNET Solutions SAS, 91090, Lisses, France

8. EXPIRY DATE

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

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., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/805/001 (10 mL)

EU/1/12/805/002 (15 mL)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

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 (¹⁸F)
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: ToC + 7.5 h

4. BATCH NUMBER

Lot
Vial No.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

≤ 12,000 MBq at ToC (see outer packaging)

6. OTHER

Radioactive material

Advanced Accelerator Applications, 53121, Bonn, Germany

PETNET Solutions SAS, 91090, Lisses, France

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**SHIELD LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Amyvid 1,900 MBq/mL solution for injection
florbetapir (^{18}F)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution for injection contains 1,900 MBq of florbetapir (^{18}F) at date and time of calibration (ToC).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
Volume: {Z} mL
Activity: {Y} MBq in {Z} mL
ToC: {DD/MM/YYYY} {hh:mm} {Time Zone}
Vial No.

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

Advanced Accelerator Applications, 53121, Bonn, Germany

PETNET Solutions SAS, 91090, Lisses, France

8. EXPIRY DATE

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

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., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/805/003 (10 mL)

EU/1/12/805/004 (15 mL)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Amyvid 1,900 MBq/mL solution for injection
florbetapir (¹⁸F)
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: ToC + 10 h

4. BATCH NUMBER

Lot
Vial No.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

≤ 28,500 MBq at ToC (see outer packaging)

6. OTHER

Radioactive material

Advanced Accelerator Applications, 53121, Bonn, Germany

PETNET Solutions SAS, 91090, Lisses, France

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Amyvid 1,900 MBq/mL solution for injection Amyvid 800 MBq/mL solution for injection florbetapir (¹⁸F)

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise 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. See section 4.

What is in this leaflet:

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

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 (¹⁸F).

Amyvid is given to adults with memory problems so that doctors can perform a type of brain scan, called a PET scan. Amyvid, along with other brain function tests, may help your doctor find the reason for your memory problems. An Amyvid PET scan can help your doctor determine whether or not you may have β -amyloid plaques in your brain. β -amyloid plaques are deposits present in the brains of people with Alzheimer's disease, but may also be present in the brain of people with other dementias. 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 (¹⁸F) or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your nuclear medicine doctor before you are given 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 obtained from the brain scan.

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

Amyvid will not affect your ability to drive or to use machines.

Amyvid contains ethanol and sodium

This medicine contains 790 mg of alcohol (ethanol) in each 10 mL dose, which is equivalent to 11.3 mg/kg (administered to an adult with 70 kg). The amount in 10 mL of this medicine is equivalent to less than 20 mL beer or 8 mL wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine also contains up to 37 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 1.85 % of the recommended maximum daily dietary intake of sodium for an adult.

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, bleeding or pain where the injection is given or rash 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.

Reporting of side effects

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

5. How 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 1,900 MBq/mL: 1 mL of solution for injection contains 1,900 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 anhydrous 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 glass vial.

Pack size

Amyvid 1,900 MBq/mL: One multidose vial of 10 mL capacity containing 1 to 10 mL of solution, corresponding to 1,900 to 19,000 MBq at date and time of calibration.

One multidose vial of 15 mL capacity containing 1 to 15 mL of solution, corresponding to 1,900 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 8,000 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 12,000 MBq at date and time of calibration.

Marketing Authorisation Holder

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands

Manufacturer

For information on the manufacturer, see vial and shield label.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Belgique/België/Belgien

Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

България

ТП "Ели Лили Недерланд" Б.В. - България
тел. + 359 2 491 41 40

Česká republika

ELI LILLY ČR, s.r.o.
Tel: + 420 234 664 111

Danmark

Eli Lilly Danmark A/S
Tlf: +45 45 26 60 00

Deutschland

Lilly Deutschland GmbH
Tel. + 49-(0) 6172 273 2222

Eesti

Eli Lilly Nederland B.V.
Tel: +372 6 817 280

Ελλάδα

ΦΑΡΜΑΣΕΡΒ-ΛΙΑΛΛΥ Α.Ε.Β.Ε.
Τηλ: +30 210 629 4600

España

Lilly S.A.
Tel: + 34-91 663 50 00

France

Lilly France
Tél: +33-(0) 1 55 49 34 34

Hrvatska

Eli Lilly Hrvatska d.o.o.
Tel: +385 1 2350 999

Ireland

Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

Ísland

Icepharma hf.
Sími + 354 540 8000

Italia

Eli Lilly Italia S.p.A.
Tel: + 39- 055 42571

Lietuva

Eli Lilly Lietuva
Tel. +370 (5) 2649600

Luxembourg/Luxemburg

Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Magyarország

Lilly Hungária Kft.
Tel: + 36 1 328 5100

Malta

Charles de Giorgio Ltd.
Tel: + 356 25600 500

Nederland

Eli Lilly Nederland B.V.
Tel: + 31-(0) 30 60 25 800

Norge

Eli Lilly Norge A.S.
Tlf: + 47 22 88 18 00

Österreich

Eli Lilly Ges.m.b.H.
Tel: + 43-(0) 1 711 780

Polska

Eli Lilly Polska Sp. z o.o.
Tel: +48 22 440 33 00

Portugal

Lilly Portugal Produtos Farmacêuticos, Lda
Tel: + 351-21-4126600

România

Eli Lilly România S.R.L.
Tel: + 40 21 4023000

Slovenija

Eli Lilly farmacevtska družba, d.o.o.
Tel: +386 (0)1 580 00 10

Slovenská republika

Eli Lilly Slovakia s.r.o.
Tel: + 421 220 663 111

Suomi/Finland

Oy Eli Lilly Finland Ab
Puh/Tel: + 358-(0) 9 85 45 250

Κύπρος
Phadisco Ltd
Τηλ: +357 22 715000

Sverige
Eli Lilly Sweden AB
Tel: + 46-(0) 8 7378800

Latvija
Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā
Tel: +371 67364000

United Kingdom (Northern Ireland)
Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

This leaflet was last revised in {MM/YYYY}.

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

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

The complete SmPC of Amyvid is provided as a separate document in the medicinal 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}.