

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neuraceq 300 MBq/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 300 MBq of florbetaben (^{18}F) at the date and time of calibration.

The activity per vial ranges from 300 MBq to 3000 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 up to 1.2 g of ethanol and up to 33 mg of sodium per dose (see section 4.4).

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.

Neuraceq 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. Neuraceq 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 florbetaben (^{18}F) should be requested by clinicians experienced in the clinical management of neurodegenerative disorders.

Neuraceq images should only be interpreted by readers trained in the interpretation of PET images with florbetaben (^{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).

Posology

The recommended activity for an adult is 300 MBq florbetaben (^{18}F). The maximum dose should not exceed 360 MBq and not fall below 240 MBq at time of administration. The volume of Neuraceq to be

injected can be from 0.5 to 10 mL in order to provide the target activity of 300 MBq at the time of intravenous administration.

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 florbetaben (^{18}F) in patients with renal or hepatic impairment has not been characterised.

Paediatric population

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

Method of administration

Neuraceq is for intravenous use and for multidose use.

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

Neuraceq should not be diluted.

The dose is administered by intravenous slow bolus injection (6 sec/mL) followed by a flush of approximately 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose. If the injection volume ranges between 0.5 and 1 mL, only syringes of an appropriate size (1 mL) should be used and the syringe needs to be flushed out with sodium chloride solution (see section 12).

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

Image acquisition

A 20-minute PET image should be acquired starting at approximately 90 minutes after intravenous injection of florbetaben (^{18}F).

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

Renal impairment and hepatic impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. Florbetaben (^{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 Neuraceq images

Neuraceq images should only be interpreted by readers trained in the interpretation of PET images with florbetaben (^{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 and false positives, have been observed.

PET images are read in a transaxial orientation using a grey scale. The reader should compare the cortical grey matter signal intensity to the maximum white matter signal intensity. The images should be viewed in a systematic manner (Figure 1) starting at the level of cerebellum and scrolling up through the lateral temporal and frontal lobes, then to the area of the posterior cingulate cortex and precuneus, and finally to the parietal lobe.

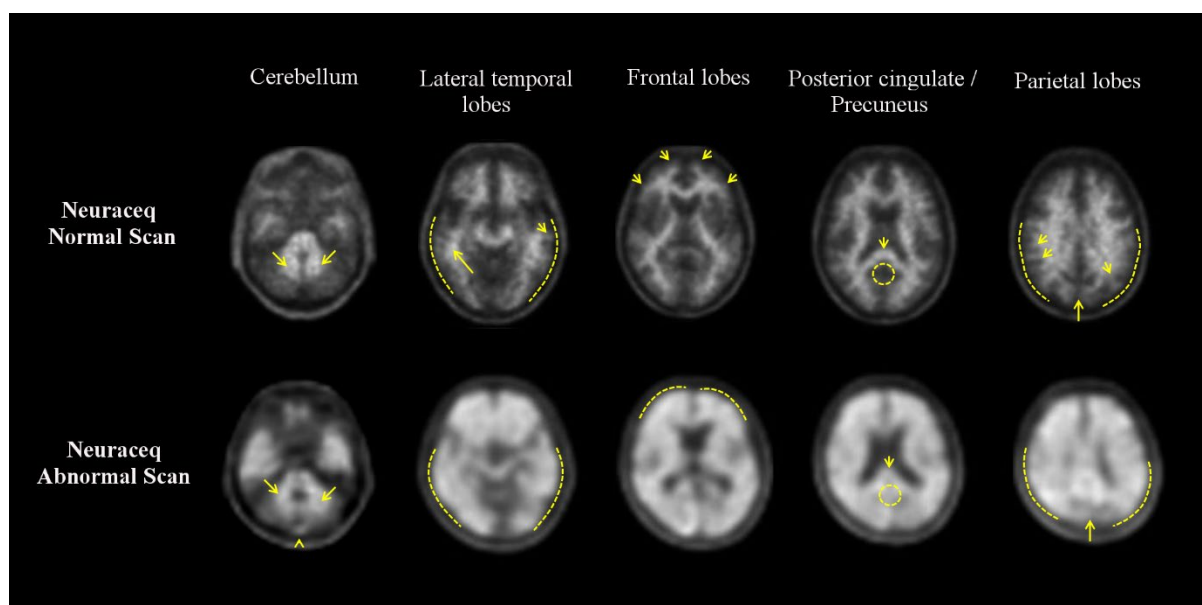
Interpretation of the images is made visually comparing the activity in cortical grey matter with activity in adjacent cortical white matter. Each of these brain regions, the lateral temporal, frontal, posterior cingulate, precuneus, and parietal lobes should be systematically visually assessed and scored according to the regional cortical tracer uptake (RCTU) score (Table 1).

Table 1: Definitions of regional cortical tracer uptake (RCTU)

RCTU score	Condition for assessment
1 (No tracer uptake)	Tracer uptake (i.e., signal intensity) in grey matter in the region is lower than in white matter.
2 (Moderate tracer uptake)	Smaller area(s) of tracer uptake equal to or higher than that present in white matter: extending beyond the white matter rim to the outer cortical margin involving the majority of the slices within the respective region.
3 (Pronounced tracer uptake)	A large confluent area of tracer uptake equal to or higher than that present in white matter extending beyond the white matter rim to the outer cortical margin and involving the entire region including the majority of slices within the respective region.

Note: For a score of tracer uptake in the cortex, the finding should have been present in the majority of the slices within the region in question.

Figure 1: Neuraceq PET cases showing examples of negative florbetaben (^{18}F) PET scan (top row) and positive scan (bottom row).



The overall decision of the visual PET scan assessment is subject-based and based on a binary outcome as ‘positive’ or ‘negative’. A subject is classified as “positive” or “negative” based on the brain amyloid plaque load (BAPL) score (Table 2) which is derived from RCTU scores in the four brain regions (Table 1).

Table 2: Definitions of brain amyloid plaque load (BAPL)

Assessment	BAPL score		Rule for assessment
Negative scan	1	Scan without beta-amyloid deposition	RCTU score 1 in each of the 4 brain regions (lateral temporal lobes, frontal lobes, posterior cingulate/precuneus, parietal lobes)
	2	Scan with moderate beta-amyloid deposition	RCTU score 2 in any or all of the 4 brain regions and no score 3 in these 4 brain regions
Positive scan	3	Scan with pronounced beta-amyloid deposition	RCTU score 3 at least in one of 4 brain regions

Use of quantitative information as an adjunct to visual assessment

Quantitative information generated by CE-marked image quantitation software for the quantification of amyloid-beta PET scans can be used as an adjunct to visual interpretation (see section 5.1). Users of the CE-marked software should be trained by the manufacturer and perform quantification according to the manufacturer’s instructions, including quality checks of the quantitative process. Readers should visually interpret the scan and then compare the quantitation result with typical ranges for negative and positive scans. If the quantitation values are inconsistent with the visual assessment, the reader should review the following aspects:

1. When applicable, region of interest (ROI) placement on the grey matter regions of the brain without including significant areas of the white matter or CSF should be examined. The potential impact of atrophy and ventricular enlargement on quantitation should be considered.

2. The placement of the reference region ROI(s), when applicable, should be examined to confirm the fit of the region. The potential impact of possible structural abnormalities on quantitation should be considered.
3. The basis for making a visual positive or negative determination should be reviewed:
 - a. In case of an amyloid positive initial visual read and negative quantitation, the reader should consider whether the positive visual interpretation might be based on tracer retention in regions not assessed by the quantitative software. A focal uptake may also return a negative quantitation when the software assesses a large region. Severe atrophy may also lead to a reduction of signal and negative quantitative results.
 - b. In the case of an amyloid negative initial visual read and an amyloid positive quantitation, the accurate positioning of the ROIs in reference regions and the cortex should be checked to determine whether white matter is sampled which may increase quantitation values.
4. A final interpretation of the PET image should be based on the visual read having conducted the review summarized in steps 1 to 3.

Limitations of use

A positive scan does not independently establish a diagnosis of AD or other cognitive disorder since neuritic plaque deposition in grey matter may be present in asymptomatic elderly and some neurodegenerative dementias (AD, 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 florbetaben (^{18}F) for predicting development of AD or monitoring response to therapy has not been established (see section 5.1).

Some scans may be difficult to interpret due to image noise, atrophy with a thinned cortical ribbon, or image blurs, 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 face, scalp and bone in some cases. Residual activity in the midsagittal sinus can be sometimes observed (see section 5.2).

After the procedure

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

Specific warnings

This medicinal product contains up to 33 mg sodium per dose, equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

A dose of 360 MBq of this medicine administered to an adult weighing 70 kg would result in exposure to up to 17 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 2.9 mg/100 ml.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

For precautions with respect to environmental hazard, see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed.

In radioligand binding assays using a broad panel of animal and human receptors, ion channels and transporters no significant binding was found.

In vitro studies using human liver microsomes did not indicate any potential to inhibit the cytochrome P450 enzyme system.

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 in florbetaben (^{18}F) (see section 5.3).

Breast-feeding

It is unknown whether florbetaben (^{18}F) is excreted in human milk. 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 fertility studies have been performed.

4.7 Effects on ability to drive and use machines

Neuraceq has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Neuraceq is based on data from 1,295 administrations of Neuraceq to 1,077 subjects and 12 subjects who received vehicle. Repeat dosing in yearly intervals showed that there was no difference in safety profile after first, second or third dosing.

Tabulated list of adverse reactions

The adverse reactions are ranked under heading of frequency using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: List of adverse reactions

System Organ Class	Common	Uncommon
Nervous system disorders		Neuralgia Headache Burning sensation Tremor
Vascular disorders		Hypotension Flushing Haematoma
Gastrointestinal disorders		Diarrhoea Nausea
Hepatobiliary disorders		Hepatic function abnormal
Skin and subcutaneous tissue disorders		Toxic skin eruption Rash Hyperhidrosis
Musculoskeletal and connective tissue disorders		Pain in extremity Limb discomfort
General disorders and administration site conditions	Injection site pain Injection/application site erythema	Pyrexia Fatigue Feeling hot Vessel puncture site pain Catheter site pain Injection site haematoma Injection site irritation Puncture site reaction Injection site discomfort Injection site warmth
Investigations		Blood creatinine increased

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is about 5.8 mSv when the maximum recommended activity of 300 MBq of florbetaben (^{18}F) is administered, these adverse reactions are expected to occur with a 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 florbetaben (^{18}F) in each dose, overdose is not expected to result in pharmacological effects. In the event of administration of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defecation. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, central nervous system;
ATC code: V09AX06

Mechanism of action

Florbetaben (^{18}F) binds to β -amyloid neuritic plaques in the brain. *In vitro*, florbetaben (^{18}F) shows nanomolar binding affinity to synthetic β -amyloid fibrils and to AD brain homogenate. In addition, binding of florbetaben (^{18}F) to β -amyloid plaques in post-mortem AD brain sections was demonstrated by autoradiography and supported by immunohistochemistry or Bielschowsky stain.

In vivo, quantitative correlation was not assessed in end-of-life patients between florbetaben (^{18}F) uptake in cortical grey matter and the beta-amyloid deposition in autopsied samples. The *in vivo* binding of florbetaben (^{18}F) to other amyloid structures or other brain structures or receptors remains unknown.

Pharmacodynamic effects

At the low chemical concentrations present in Neuraceq, florbetaben (^{18}F) does not have any detectable pharmacodynamic activity.

In completed clinical trials, uptake of florbetaben (^{18}F) in 7 predefined cortical areas of the brain (frontal, parietal, lateral and medial temporal, occipital, caudate, posterior cingulate/precuneus cortex, and anterior cingulate gyrus) and cerebellar cortex was measured quantitatively using standardised uptake values (SUV). Cortical SUV ratios (SUVRs, relative to cerebellar cortex) are higher in AD patients compared with those of healthy volunteer subjects.

Clinical efficacy

A pivotal study in 31 end-of-life patients was aimed at establishing the diagnostic performance of florbetaben (^{18}F) to detect the cortical neuritic plaque density (no or sparse vs. moderate or frequent) as established by the CERAD criteria. The PET results were compared with the maximal neuritic plaque density measured on sections of middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobe, hippocampus and other brain regions at the patient's autopsy. The cognitive status of the subjects could not be determined reliably. In all 31 subjects, a blinded visual subject-level PET reading by 3 blinded readers resulted in a majority read sensitivity of 100% (95% CI: 80.5-100%) and specificity 85.7% (95% CI: 67.4 - 100%). In a post-hoc analysis sensitivity and specificity of the majority read of the visual subject-level PET reading vs histopathology in a larger population (74 patients) was 97.9% (95% CI: 93.8 - 100%) and 88.9% (95% CI: 77-100%).

Sensitivity and specificity to estimate beta-amyloid deposition of florbetaben (^{18}F) was further investigated in one additional study, in which a different set of 5 electronically-trained blinded readers interpreted images from 54 subjects followed to autopsy in the pivotal study. The histopathology criteria did not match the CERAD criteria. The results were lower than the results obtained in the pivotal trial: a sensitivity range between 77.5% to 90% and specificity range between 62.5-85.7%. Inter-rater agreement using Fleiss' kappa values ranged from 0.68 to 0.87. Comparing the results of PET scan reading with the histopathology assessment collected for all subjects (same as used for the original pivotal study and its post-hoc analysis), the majority read sensitivity and specificity were 100% (95%CI: 89.4-100%) and 71.4% (95%CI: 52.1-90.8%), respectively.

In a longitudinal study, 45 subjects clinically diagnosed with mild cognitive impairment (MCI), underwent baseline florbetaben (^{18}F) PET scans, and were followed for 24 months to evaluate the relationship between florbetaben (^{18}F) imaging and changes in diagnostic status. 29 (64.4%) of MCI patients were positive by florbetaben (^{18}F) PET scan. At the 24-month follow-up, 19 (42.2%) converted to clinical AD. Of the 29 MCI subjects who had a positive PET scan, 19 (65.5%) were classified clinically as converted to clinical AD after 24 months compared to 0 (0%) of 16 who had a negative scan. Sensitivity of florbetaben (^{18}F) scan to show the MCI conversion rate to AD in 19 converters was 100%, specificity in 26 non-converters was 61.5% (95% CI: 42.8-80.2%) and

positive likelihood ratio was 2.60 (1.60-4.23). 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 reliability of using quantitative information as an adjunct to visual inspection was analysed in a retrospective clinical study, which assessed (i) the diagnostic performance (i.e., sensitivity and specificity) of the quantitative assessment of florbetaben PET scans against the histopathological confirmation in the detection of beta-amyloid neuritic plaques in the brain of end-of-life patients (n=81) and young cognitively normal healthy controls (n=10) and (ii) the concordance between visual majority read of five independent blinded readers and quantitative assessment of florbetaben PET scans (n=386). Three CE-marked software packages using the whole cerebellum as reference region were used to estimate amyloid-beta load with standardized uptake value ratios (Hermes Brass v.5.1.1, Neurocloud v.1.4) or centiloids (MIMneuro v.7.1.2). All scans were quality controlled to ensure correct positioning of regions of interest; cases that did not pass quality control were excluded from the analysis (on average 2.6% of the cases analysed with CE-marked software). The mean sensitivity and specificity in three CE-marked amyloid quantitation software packages was 95.8±1.8% and 98.1±1.4%, respectively. The thresholds for amyloid quantitation were derived from samples with post-mortem confirmation of brain amyloid status as the standard of truth (from pivotal clinical autopsy cohort) using receiver operating characteristics (ROC) curve analysis. In a second dataset, the derived thresholds were used to categorise a test cohort and to compare the binary quantitative assessment and visual read. In a quality checked dataset, the average concordance between visual read and the CE-marked software packages was 91.2±1.7% and 96.2±1.8% in a subset where a group of readers had consensus in the visual assessment, i.e., all readers assessed the scans in the same way.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with florbetaben (¹⁸F) in all subsets of the paediatric population as the disease or condition for which the specific medicinal product is intended only occurs in adult population, and the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution

After intravenous bolus injection a radioactivity concentration of 2-3% injected dose/L is achieved in arterial plasma 10 minutes after injection.

Florbetaben (¹⁸F) is highly bound to plasma proteins (>98.5%).

Organ uptake

Uptake of radioactivity in the brain is rapid, reaching about 6% of injected radioactivity at 10 minutes post injection.

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

Uptake has also been identified in some cases in extracerebral structures such as face, scalp and bone. The reason for this accumulation is unknown, but maybe due to accumulation of florbetaben (¹⁸F) or to any of its radioactive metabolites, or to blood radioactivity. Residual activity in the midsagittal sinus can be sometimes observed likely due to the presence of tracer in the blood pool.

The biophysical basis of the white matter retention of florbetaben (¹⁸F) in the living human brain cannot be definitively explained. It is hypothesised that unspecific binding of the radiopharmaceutical to the lipid-containing myelin sheath may contribute to white matter retention.

Elimination

Florbetaben (^{18}F) is eliminated from plasma of AD patients with a mean biological half-life of about 1 hour. No radioactivity could be measured in blood at about 4 hours post injection. Based on *in vitro* investigations florbetaben (^{18}F) is metabolised predominantly by CYP2J2 and CYP4F2.

At 12 hours post-injection, up to approximately 30% of the injected radioactivity is excreted with urine. Time points beyond that time frame did not allow for further quantitation of activity in urine.

Half-life

Fluorine (^{18}F) has a physical half-life of 110 minutes.

At 12 hours post injection 98.93% of the activity is decayed, at 24 hours post injection 99.99 % of the activity is decayed.

Renal/hepatic impairment

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. The potential toxicity of 28 days of repeated intravenous injections of florbetaben (^{18}F) was tested in rats and dogs, and the NOAEL was found to be at least 20 times the maximum human dose.

Chronic studies and carcinogenicity studies have not been carried out, since the medicinal product is not intended for regular or continuous administration.

Studies on reproduction toxicity have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid
Ethanol anhydrous
Macrogol 400
Sodium ascorbate (for pH adjustment)
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

Up to 10 hours from the end of the synthesis.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Colourless 15 mL Type I glass vial, sealed with a chlorobutyl stopper and aluminium seal.

Each multidose vial contains 1 to 10 mL of solution, corresponding to 300 to 3000 MBq at the date and time of calibration (ToC).

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

Pack size: one 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Berlin
13353
Germany
e-mail: gra@life-mi.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/906/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20. February 2014

Date of latest renewal: 20. November 2018

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The table below shows the dosimetry as calculated using the OLINDA (Organ Level Internal Dose Assessment) software.

The estimated absorbed radiation doses to organs are listed in Table 4, providing data from Caucasian healthy volunteers (n=17). Dosimetry calculations were adapted to the adult model (with a body weight of 70 kg).

Table 4: Estimated radiation absorbed doses from intravenous injection of Neuraceq to Caucasian subjects

Organ	Dose absorbed per activity administered [mGy/MBq]
Adrenal	0.0130
Brain	0.0125
Breasts	0.0074
Gallbladder	0.137
Gastrointestinal tract	
Lower large intestine	0.0351
Small intestine	0.0314
Stomach	0.0116
Upper large intestine	0.0382
Heart	0.0139
Kidneys	0.0238
Liver	0.0386
Lungs	0.0148
Muscles	0.00948
Ovaries	0.0156
Pancreas	0.0139
Red marrow	0.0122
Osteogenic cells	0.0148
Skin	0.00689
Spleen	0.0102
Testes	0.00913
Thymus	0.00892
Thyroid	0.00842
Bladder	0.0695
Uterus	0.0163
Remaining organs	0.0110
Effective dose (mSv/MBq)	0.0193

The effective dose resulting from the administration of a maximal recommended activity of 360 MBq dose for an adult weighing 70 kg is about 7.0 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 360 MBq the typical radiation dose to the target organ (brain) is 4.5 mGy.

For an administered activity of 360 MBq the typical radiation doses delivered to the critical organs, gallbladder, urinary bladder, upper large intestine wall, lower large intestine wall, small intestine and liver are 49.3 mGy, 25.0 mGy, 13.8 mGy, 12.6 mGy, 11.3 mGy and 13.9 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. If the integrity of the vial is compromised, the medicinal product should not be used.

Florbetaben (18F) should not be diluted.

The dose is administered by intravenous slow bolus injection (6 sec/mL) followed by a flush of approximately 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure full delivery of the dose. If the injection volume ranges between 0.5 and 1 mL, only syringes of an appropriate size (1 mL) should be used and the syringe needs to be flushed out with sodium chloride solution.

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

Quality control

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

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

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

BV Cyclotron VU
De Boelelaan 1081
1081 HV Amsterdam
The Netherlands

Curium PET France
CHU Brabois
4 rue du Morvan
54500 Vandoeuvre les Nancy
France

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

Curium PET France
14 rue de la Grange aux Belles
75010 Paris
France

Curium PET France
avenue de la Bataille Flandres Dunkerque, CS 44229
35000 Rennes
France

Curium PET France
CHU Xavier Arnozan
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33604 Pessac
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Alliance Medical RP Berlin GmbH
Max-Planck-Strasse 4
Adlershof
Berlin
12489
Germany

Alliance Medical RP sp. z o.o.
ul. Szeligowska 3
05-850 Szeligi
Poland

Alliance Medical RP GmbH
Spessartstr. 9
53119 Bonn
Germany

Curium Italy S.R.L.
via Pergolesi, 33
20900 Monza
Italy

Curium Italy S.R.L.
Viale Oxford 81 (loc. Tor Vergata)
00133 Rome
Italy

Curium Italy S.R.L.
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33100 Udine
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ITEL Telecomunicazioni S.R.L.
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70037 Ruvo di Puglia (BA)
Italy

Curium Pharma Ireland Limited
Blackrock Clinic
Blackrock
Co. Dublin, A94 E4X7
Ireland

Curium Pharma Spain, S.A.
Thomas Alba Edison, s/n
41092 Seville
Spain

Curium Pharma Spain, S.A.
Pol. Ind. Conpisa, C/ Veguillas, 2 Nave 16,
Ajalvir 28864 (Madrid)
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Seibersdorf Labor GMBH
Grundstueck Nr. 482/2 EZ 98 KG
2444 Seibersdorf
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1200 Brussels
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Institut Radiofarmacia Aplicada Barcelona-IRAB
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08003 Barcelona
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Biokosmos S.A.
Lakkoma Industrial Area
Nea Propontida
Halkidiki
630 80
Greece

Biokosmos S.A.
Thesi Panormos
Lavrio
Athens
195 00
Greece

Radboud Translational Medicine B.V.
Geert Grooteplein Noord 21
Route 142
Nijmegen
Gelderland
6525 EZ
Netherlands

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

The requirement for submission of periodic safety update report for this medicinal product are set out in the line of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2011/83/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 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 Marketing Authorisation Holder (MAH) shall agree the final educational programme with the National Competent Authority.

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

The training programme should contain the following key elements:

- Information on amyloid pathology in Alzheimer's disease;
- Relevant information on Neuraceq as an β -amyloid PET tracer, including the approved indication according to the SmPC, limitations of Neuraceq use, interpretation errors, safety information and the results of clinical trials informing on the diagnostic use of Neuraceq;
- Review of the PET reading criteria, including method of image review, criteria for interpretation, and images demonstrating the read methodology;
- The training material should include Neuraceq PET demonstration cases with correct PET scan interpretation by an experienced reader Neuraceq-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 should be ensured.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**METAL BOX /LEAD SHIELDING CONTAINER****1. NAME OF THE MEDICINAL PRODUCT**

Neuraceq 300 MBq/mL solution for injection
florbetaben (^{18}F)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution for injection contains 300 MBq of florbetaben (^{18}F) at the date and time of calibration.

3. LIST OF EXCIPIENTS

Ascorbic acid, ethanol anhydrous, macrogol 400, sodium ascorbate (for pH adjustment), water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
One multi-dose vial
Customer ref

Activity: {XXX} MBq in {XX} mL

ToC: {DDMMYYYY} {XX}h{XX} {Time zone}

Volume: {XX} mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Radioactive material.

BV Cyclotron VU, the Netherlands

Curium PET France, Nancy, France

Curium PET France, Nîmes, France

Curium PET France, Paris, France

Curium PET France, Rennes, France

Curium PET France, Pessac, France

Alliance Medical RP Berlin GmbH, Germany

Alliance Medical RP sp. z o.o., Poland

Alliance Medical RP GmbH, Germany

Curium Italy S.R.L., Monza, Italy

Curium Italy S.R.L., Rome, Italy

Curium Italy S.R.L., Udine, Italy

Curium Pharma Spain, S.A., Seville, Spain

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

Seibersdorf Labor GmbH, Austria

BetaPlus Pharma SA, Brussels, Belgium

Institut Radiofarmacia Aplicada Barcelona-IRAB, Barcelona, Spain

ITEL Telecomunicazioni S.R.L., Bari, Italy

Curium Pharma Ireland Limited, Dublin, Ireland

Biokosmos S.A., Halkidiki, Greece

Biokosmos S.A., Athens (Lavrio), Greece

Radboud Translational Medicine B.V., Nijmegen, Netherlands

8. EXPIRY DATE

EXP {DD/MM/YYYY} {XX}h{XX} {Time zone}

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from ionising radiation (lead shielding).

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Life Molecular Imaging GmbH, Tegeler Strasse 6-7, Wedding, Berlin, 13353, Germany

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/13/906/001

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>

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

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

Neuraceq 300 MBq/mL solution for injection
florbetaben (^{18}F)
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP: ToC + 6 h

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Act.: ≤ 3000 MBq at ToC (see outer label)

6. OTHER



Radioactive material.

BV Cyclotron VU, the Netherlands

Curium PET France, Nancy, France

Curium PET France, Nîmes, France

Curium PET France, Paris, France

Curium PET France, Rennes, France

Curium PET France, Pessac, France

Alliance Medical RP Berlin GmbH, Germany

Alliance Medical RP sp. z o.o., Poland

Alliance Medical RP GmbH, Germany

Curium Italy S.R.L., Monza, Italy

Curium Italy S.R.L., Rome, Italy

Curium Italy S.R.L., Udine, Italy

Curium Pharma Spain, S.A., Seville, Spain

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

Seibersdorf Labor GmbH, Austria

BetaPlus Pharma SA, Brussels, Belgium

Institut Radiofarmacia Aplicada Barcelona-IRAB, Barcelona, Spain

ITEL Telecomunicazioni S.R.L., Bari, Italy

Curium Pharma Ireland Limited, Dublin, Ireland

Biokosmos S.A., Halkidiki, Greece

Biokosmos S.A., Athens (Lavrio), Greece

Radboud Translational Medicine B.V., Nijmegen, Netherlands

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Neuraceq 300 MBq/mL solution for injection florbetaben (^{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. See section 4.

What is in this leaflet:

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

1. What Neuraceq is and what it is used for

This medicine is a radiopharmaceutical product for diagnostic use only.

Neuraceq contains the active substance florbetaben (^{18}F).

Neuraceq is given to people with memory problems so that doctors can perform a type of brain scan, called a PET scan. A Neuraceq 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 Neuraceq does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit of this procedure with the radiopharmaceutical outweighs the risk of being exposed to radiation.

2. What you need to know before Neuraceq is used

Neuraceq must not be used:

- if you are allergic to florbetaben (^{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 Neuraceq if you:
have kidney problems

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

Children and adolescents

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

Other medicines and Neuraceq

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 from the PET scan.

Pregnancy and breast-feeding

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 advise before you are given this medicine.

You must inform the nuclear medicine doctor before you are given Neuraceq 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.

Pregnant

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

Breast-feeding

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

Driving and using machines

Neuraceq has no influence on the ability to drive and use machines.

Neuraceq contains ethanol and sodium ascorbate

- This medicine contains up to 1200 mg of alcohol (ethanol) in each dose, which is equivalent to 17 mg/kg. The amount per dose of this medicine is equivalent to 30 ml beer or 12.5 ml wine.

The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy.

The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

If you are pregnant or breastfeeding, talk to your doctor or pharmacist before taking this medicine.

If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

- This medicine contains up to 33 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 1.6% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Neuraceq will be used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Neuraceq will only be used in specially controlled areas. This medicine will only be handled and given to you by professionals 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 amount of Neuraceq to be used in your case. It will be the smallest amount necessary to get the desired information.

The quantity to be administered usually recommended for an adult is 300 MBq (megabecquerel, the unit used to express radioactivity).

Administration of Neuraceq and conduct of the procedure

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

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

Duration of the procedure

A brain scan is usually taken 90 minutes after Neuraceq is given.

Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of Neuraceq, you should:

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

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

If you have been given more Neuraceq than you should

An overdose is unlikely since you will only receive a single dose of Neuraceq 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 questions on the use of this medicine, please ask your nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible side effects include:

Common (may affect up to 1 in 10 people):

- Injection site reactions: injection site pain, redness of the skin at injection site (injection / application site erythema)

Uncommon (may affect up to 1 in 100 people):

- Burning sensation, headache, neuralgia (intense, typically intermittent pain along the course of a nerve), tremor (an involuntary quivering movement)
- Vessels: flushing (sudden reddening of the face and/or neck), haematoma (a bruise, a black and blue mark), hypotension (low blood pressure)
- Stomach: diarrhea, nausea (feeling sick)
- Liver: abnormal liver function
- Skin: hyperhidrosis (excessive sweat), rash, toxic skin eruption (acute skin affections with measles-type erythema of the skin, potentially including blisters and ulcerations)
- Muscles and bones: limb discomfort, pain in extremity
- Injection site conditions: injection site irritation, pain and discomfort around the injection site, injection site haematoma (a bruise, a black and blue mark at injection site), injection site warmth, tiredness, feeling hot, pyrexia (raised body temperature, a fever)
- Abnormal blood test: increased blood creatinine levels (reduced kidney function)

This radiopharmaceutical will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities.

Reporting of side effects

If you get any side effects please talk to your nuclear medicine doctor. This includes any 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 Neuraceq 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:

- Keep out of the sight and reach of children.
- Do not use after the expiry date which is stated on the box, shield label and vial label after EXP.
- This medicine does not require any special storage conditions.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Neuraceq contains

- The active substance is florbetaben (^{18}F). Each mL of solution for injection contains 300 MBq of florbetaben (^{18}F) at the date and time of calibration. The activity per vial ranges from 300 MBq to 3000 MBq at the date and time of calibration.
- The other ingredients are ascorbic acid, ethanol anhydrous, macrogol 400, sodium ascorbate, and water for injections (see section 2 “Neuraceq contains ethanol and sodium ascorbate”).

What Neuraceq looks like and contents of the pack

Neuraceq is a clear, colourless solution for injection. It is supplied in a colourless 15 mL glass vial, sealed with a rubber stopper and aluminium seal.

Each multidose vial contains 1 to 10 mL of solution, corresponding to 300 to 3000 MBq of florbetaben (^{18}F) at the date and time of calibration.

Pack size of 1 vial.

Marketing Authorization Holder

Life Molecular Imaging GmbH
Tegeler Strasse 6-7
Wedding
Berlin
13353
Germany
e-mail: gra@life-mi.com

Manufacturer

BV Cyclotron VU
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1081 HV Amsterdam
The Netherlands

Curium PET France
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Curium PET France
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Curium PET France
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Gelderland
6525 EZ
Netherlands

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

This leaflet was last revised in {month YYYY}.

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

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

The complete SmPC of Neuraceq 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}.