Neuraceq 300 MBq/mL solution for injection

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 (18F) 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 (18F). 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 (18F) 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 (18F) 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 (18F) 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 (18F).

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 (18F). 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.

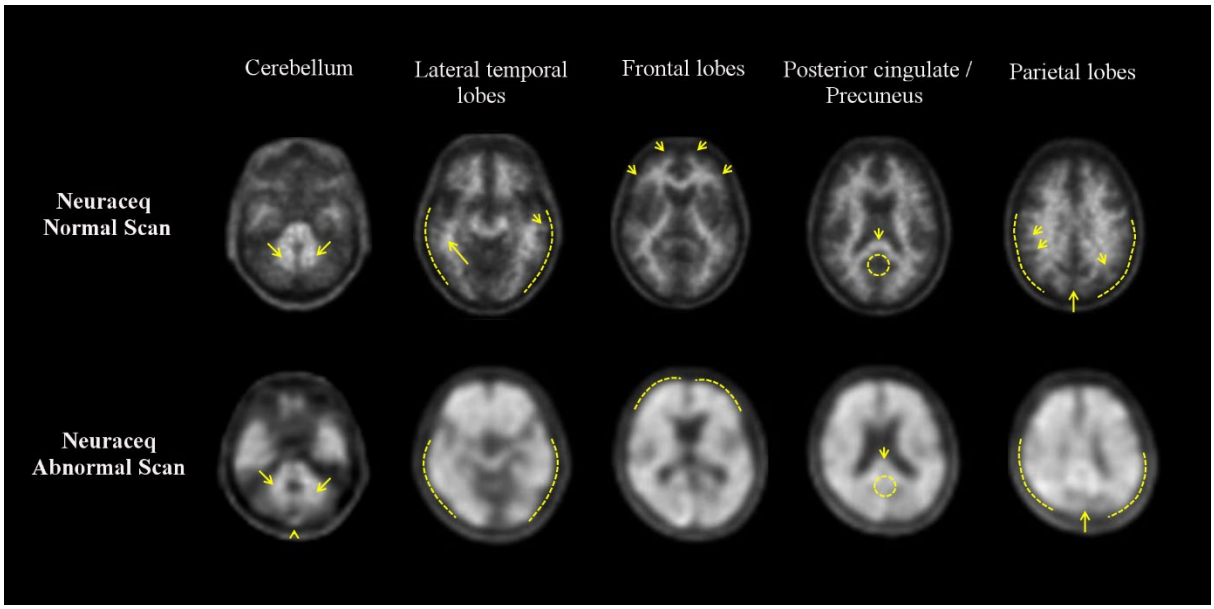
Interpretation of the images is made visually comparing the activity in cortical grey matter with activity in adjacent cortical white matter. Each of these brain regions, the lateral temporal, frontal, posterior cingulate, precuneus, and parietal lobes should be systematically visually assessed and scored 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)
Positive scan	**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
	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* binding assays using amyloid-targeting antibodies did not indicate any interactions, consistent with distinct binding sites.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the

available data). 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.

Ireland

HPRA Pharmacovigilance
Website: www.hpra.ie

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 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 (^{18}F) in all subsets of the paediatric population as the disease or condition for which the specific medicinal product is intended only occurs in 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 (^{18}F) 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 (^{18}F) 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 (^{18}F) 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 (^{18}F) 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

Life Molecular Imaging GmbH
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Wedding
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

07/2025

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

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13353
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