EU Risk Management Plan for Neuraceq (florbetaben (^{18}F))

RMP Version number: 7.0

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Rationale for submitting an updated RMP: Removal of the important potential risk "PET scan interpretation errors" and subsequently removal of the additional risk minimisation measure in the form of educational material

Summary of significant changes in this RMP:

- Tabulated summary of changes per module

Module	Changes
Title page and throughout the document	Update version number to 7.00 and version date
QPPV, MAH, MAH logo	Updated
Part I, Part II	Indication updated
Part II, SI.1	Epidemiology of the disease updated. Treatment options added. Information on mortality and morbidity updated
Part II SI.2	Amyloid lowering medicines added as concomitant medication
PART II SSV	SV.1.2 Exposure and SV.2 off-label use updated
Part II, SIV.2	Update of information due to prolonged exposure
Part II, SV.3	Information on patients with cardiovascular impairment and immunocompromised patients provided
Par II, SVI	The potential for misuse or illegal purposes briefly discussed
Part II, SVII.3.1 and throughout the document	The important potential risk "PET scan interpretation errors" removed
Part V, V.1 and V.2 and throughout the document	The additional risk minimisation measure in the form of educational material (training of PET scan readers) removed
Part VI, SII, SII.A, SII.B and SII.C.2	Sentence pointing to the "missing information" section deleted. List of important risks and risk minimisation measures updated. Sentence amended for other studies in post-authorisation development plan.
Annex 6	Key messages of the additional risk minimisation measures removed

Other RMP versions under evaluation: No

Details of the currently approved RMP:

- Summary of safety concerns:

Important identified risks	None
Important potential risks	None
Important missing information	None

- Pharmacovigilance Plan

  Routine pharmacovigilance activities that include adverse reaction management, signal management, and other routine PV activities as per GVP.

- Version number: 7.0
- Approved with procedure: EMA/VR/0000227744
- Date of approval (opinion date): 24 Jul 2025

QPPV name: Meike Dahlke

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Florbetaben (^{18}F)
Pharmacotherapeutic group(s) (ATC Code)	V09AX06: diagnostic radiopharmaceutical, central nervous system
Marketing Authorisation Holder	Life Molecular Imaging GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Neuraceq
Marketing authorisation procedure	centralised
Brief description of the product	Chemical class: Florbetaben (^{18}F) is a radiopharmaceutical [^{18}F]-labelled polyethylenglycol (PEG) stilbene derivative
	Summary of mode of action: Florbetaben (^{18}F) binds specifically to beta-amyloid deposits with high affinity.
	Important information about its composition: NA
Hyperlink to the Product Information	Latest approved Product Information
Indication(s) in the EEA	Current: Florbetaben (^{18}F) is 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 of the SmPC.
	Proposed: NA

Dosage in the EEA	Current: 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.
	Proposed: NA
Pharmaceutical form(s) and strengths	Current: solution for injection (300 MBq/ml)
	Proposed: NA
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Neuraceq is a radiopharmaceutical indicated for PET imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for 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 SmPC sections 4.4 and 5.1.

SI.1 Epidemiology of the disease

Incidence, prevalence and demographic profile of target population

AD is a progressive and ultimately fatal neurodegenerative condition. Compared to patients without dementia, individuals with AD face a fourfold increase in mortality risk and have an average life expectancy of six years following diagnosis [1].

Its prevalence markedly increases with age, becoming an increasing public health topic in an ageing population. According to European estimates, there are 6.9 million individuals diagnosed with AD dementia, 15 million individuals in the prodromal stage of AD, and 52 million individuals in the preclinical stage of AD. Collectively, these figures represent 25% of the European population aged 50 and above [2].

Risk factors for the disease

AD is a progressive disease, meaning that damage to neurons, and in turn the resulting cognitive impairment, worsens with time. Because of this, age proves to be the biggest risk factor for AD, with five percent of people age 65 to 74, 13.1% of people age 75 to 84, and 33.3% of people age 85 or older have Alzheimer's dementia [3].

Clinical course of disease

The clinical progression of AD is characterized by worsening memory loss, behavioural changes, gait and motor disturbances, and a decreasing capacity to perform activities of daily living. Ultimately, patients become entirely dependent on caregivers, often leading to the need for nursing home care and eventually resulting in death [4]. No patient has ever recovered from AD. The gradual loss of independence in patients with AD imposes a significant burden on caregivers, families, and society as a whole [3].

An earlier and more accurate diagnosis can be facilitated by using biomarkers, e.g. Amyloid PET, for the detection of a particular pathology. Improving the diagnosis has important implications as may leads to changes of the etiological diagnosis, patient management and enables the development and use of new therapies.

Treatment options

Currently, the most commonly utilized treatment options for AD primarily offer temporary relief of symptoms. These treatments include acetylcholinesterase inhibitors and the N-

methyl-D-aspartate (NMDA) receptor antagonist, memantine. While both have demonstrated symptomatic benefits in patients with AD, they do not address the underlying cause of the disease nor alter its progression. A key pathological hallmark in the brain is the presence of amyloid, which is believed to initiate a cascade of events leading to the accumulation and spread of abnormally aggregated tau protein (neurofibrillary tangles). This process results in neuronal dysfunction, cognitive impairment, and ultimately, neurodegeneration and death.

Recent clinical studies have suggested that effective removal of amyloid plaques can slow the cognitive deterioration of AD. Three disease-modifying therapies have been approved by the FDA, lecanemab (Leqembi® [Eisai R&D Management Co., Ltd. Nutley, NJ, USA]), donanemab (Kisunla® [Eli Lilly and Company, Indianapolis, IN, USA] and aducanumab (Aduhelm® [Biogen, Cambridge, MA]). In Europe, lecanemab (EMEA/H/C/005966) has received a positive CHMP opinion on 14 Nov 2024. The Marketing Authorisation Application of donanemab (EMEA/H/C/006024) has received a negative CHMP opinion on 27 Mar 2024 (the applicant has requested a re-examination of the CHMP opinion) and the application for the marketing authorisation of aducanumab (EMEA/H/C/005558) was withdrawn by the marketing authorisation applicant in 2022.

Patients with cognitive impairment, their caregivers and providers deserve timely diagnosis to ensure appropriate access to disease-modifying options to treat this complex, progressive disease. This is especially important given the serious and ultimately fatal nature of AD, and the major public health burden for patients, caregivers, and society.

Mortality and morbidity and implications for public health

Advancements in healthcare over the past century have significantly extended life expectancy and improved overall well-being. Consequently, the global population is aging. However, this demographic shift has been accompanied by a rise in the prevalence of noncommunicable diseases (NCDs), such as dementia, posing new challenges for public health systems [5].

In 2019, dementias, including Alzheimer's disease, were responsible for 1.6 million deaths globally. The combination of population growth, longer life expectancy, and a likely rise in risk factors has driven a significant surge in dementia-related deaths over the past two decades. As a result, dementia and its subtypes, such as Alzheimer's disease, have become the seventh leading cause of death worldwide [5].

Alzheimer's disease may contribute to more deaths than officially reported. It is also a major cause of disability and poor health (morbidity) in older adults. Individuals with Alzheimer's often endure years of declining health and increasing disability as the disease advances before it ultimately proves fatal [3].

As the prevalence of AD continues to rise with aging populations, the associated economic costs are projected to further escalate [6].

Purpose of medicinal product

Florbetaben (^{18}F) is a diagnostic radiopharmaceutical which is 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 AD and other causes of cognitive impairment. . Neuraceq should be used in conjunction with a clinical evaluation. As a limitation of use it must be considered that 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.

Early and accurate diagnosis of AD during life is important as it facilitates correct and early implementation of all available treatment options. Knowledge of the underlying disease is reassuring to both the subject and the caregiver and aids in future planning. Unnecessary time to diagnosis and additional investigations can be avoided, and symptoms are alleviated, with a subsequent increase in quality of life for the subject and his or her family. Florbetaben (^{18}F) is indicated for use in a population which already has a decrement in cognitive function and will support diagnosis in the context of clinical signs and symptoms (including cognitive impairment).

Additionally, Neuraceq was also used in the development programs of amyloid-lowering therapies as it allowed patient selection and monitoring the beta amyloid plaques in the brain, i.e. the removal of amyloid.

SI.2 Concomitant medications in the target population

Given the target population, corresponding co-morbidities such as cardiovascular disease, diabetes, hypertension, cerebrovascular disease, hyperthyroidism, hypothyroidism and others will be common – including concomitant treatment medication. These may include e.g. calcium-channel blocker, thiazides, ACE inhibitors, angiotensin-II antagonists and beta-blocker regarding hypertension, 4-hydroxycoumarins as anticoagulants, insulin, meglitinides, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, amylin mimetics or incretin mimetics regarding diabetes, lipid-modifying agents to reduce cardiovascular risk, and thyroid hormones or antithyroid preparations for diseases affecting thyroid function. It is expected that the target population will also use Alzheimer's amyloid-targeting therapies.

SI.3 Important co-morbidities found in the target population

As the target population mainly consists of elderly patients, important co-morbidity prevalent in the elderly population (e.g. cardiovascular disease, diabetes, hypertension, cancer, ophthalmological disorders, neurological disorders, cerebrovascular disease, hyperthyroidism, hypothyroidism etc.) is typically expected.

There is some evidence that the metabolic syndrome and diabetes mellitus are associated with dementia and AD [7]. A recent systematic review of longitudinal population-based studies suggested that "the risk of dementia is, in general increased in patients with diabetes mellitus. This increased risk includes both, AD and vascular dementia." The strength of the association found varied in the range between 1.3 and 3 relative risk [8].

A prospective study revealed that hypertension was linked to AD or vascular dementia [9]. Furthermore, a raised systolic blood pressure was found to go along with reduced brain weight accompanied by neuritic (beta-amyloid) plaques in the neocortex and hippocampus [10]. Hypertension can also lead to endothelial damage resulting in impaired nitric oxide production with the development of free radicals and in triggering inflammatory responses resulting in neuritic plaque formation [11].

Thyroidal disorders like hyperthyroidism and hypothyroidism might also be a risk for dementia and seem to be linked to AD. There is evidence that high or low levels of thyroid stimulating hormone are associated with AD in female subjects [12].

In addition, the risk of fractures appears to be increased in patients with AD. The risk of hip fracture has been investigated in a cohort of Alzheimer patients identified in a study using electronic medical records from primary care practices in the UK [13] and was found to be approximately three times higher compared to patients without an AD diagnosis.

Important and common neuropsychiatric co-morbidity in AD includes major depression (prevalence up to 50 %) and psychosis (median prevalence 41 % in a review of 55 studies) [14-15].

Part II: Module SII - Non-clinical part of the safety specification

Biodistribution in male mice and dosimetry prediction

The percentages of the injected dose identified in the respective organs were extrapolated to humans using metabolic and organ mass scaling and the radiation burden was calculated using the Organ Level Internal Dose Assessment (OLINDA) software (see Table SII-1).

Osteogenic cells sustain the largest radiation absorbed dose 24.5 µGy/Mega Becquerel (MBq). The resultant total ED is 12.4 µSv/MBq. Based on the extrapolated mouse data an infusion of 300 MBq of florbetaben (^{18}F) to a 70 kg adult patient will result in an ED of 3.7 mSv. The organ doses for florbetaben (^{18}F) are comparable to those associated with other commonly performed nuclear medicine tests and indicate that potential radiation risks associated with studies using florbetaben (^{18}F) are within generally accepted limits.

Table SII-1: Radiation absorbed doses per organ and effective dose to an average adult patient (70 kg) from an intravenous dose of florbetaben (^{18}F) extrapolated from mouse data

Organ	Radiation absorbed doses (µGy/MBq)
Adrenals	9.25
Brain	5.38
Breasts	8.04
Gallbladder wall	10.5
LLI wall	16.4
Small intestine	13.5
Stomach wall	9.84
ULI wall	14.4
Heart wall	8.20
Kidneys	5.59
Liver	7.75
Lungs	7.09
Muscle	6.10

Organ	Radiation absorbed doses (µGy/MBq)
Ovaries	11.5
Pancreas	6.28
Red marrow	11.9
Osteogenic cells	24.5
Skin	6.85
Spleen	6.25
Testes	5.16
Thymus	9.16
Thyroid	6.69
Urinary bladder wall	17.0
Uterus	11.8
Total Body	9.31
Effective Dose (µS/MBq)	12.4

LLI = Lower large intestine; ULI = Upper large intestine; µGy = microGray; MBq = megaBequerel; µSv = microSievert

Toxicology

To evaluate the toxicological profile of (^{18}F) (single and repeated dose toxicity, genotoxicity, local tolerance), the **non-radioactive ^{19}F labelled analogue** of florbetaben (^{18}F) in form of its hydrochloride salt [redacted] was used. In addition, several studies for characterization of potential impurities in the clinical drug product and for characterization of decay products were performed.

Single dose toxicity

Rats and rabbits tolerated single i.v. injections without clear-cut adverse reactions at doses of up to 400 µg in rats and 250 µg/kg in rabbits representing at least 90 (rabbits) to 280 (rats) times the maximum intended human mass dose (30 to 50 µg per person) scaled for body surface area.

Repeat dose toxicity studies

Repeated dose toxicity studies over 4 weeks in rats and dogs confirmed, that florbetaben (^{19}F) hydrochloride was very well tolerated at doses of 700 µg/kg in rats and 200 µg/kg in dogs representing 120 to 200 times the intended maximum clinical mass dose based on body surface area.

Genotoxicity

The in vitro and in vivo genotoxicity assays with florbetaben (^{19}F) hydrochloride did not reveal any mutagenic potential of the drug substance.

Reproductive and developmental toxicity

Studies addressing reproductive toxicity were not performed and are not considered necessary for the intended clinical trials. There was no indication of an effect on male or female fertility in repeat-dose toxicity studies. In addition, because of the elderly patient population, treatment of women of child-bearing potential is unlikely. In women of child-bearing potential,

the use of florbetaben (^{18}F) must be weighed carefully against the risk in pregnant women. 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.

Local tolerance

The local tolerance studies with the non-radioactive clinical drug product in rabbits and dogs indicate that the i.v. injection of the clinical drug product should cause no relevant local irritation, when injected according to the recommended procedure to use larger veins and to flush the vein with saline after the injection of the drug product. Paravenous injection should be avoided because of the potential for local reaction.

Other toxicity studies

Characterization of potential impurities (precursor or reaction by-products)

The weakly mutagenic potential found with the impurity mix results in little additive risk, since the maximum amount of 1 µg of each impurity per vial is below the threshold of toxicological concern (TTC) of 1.5 µg daily for lifelong intake, as defined in EU guidance: "Guideline on the Limits of Genotoxic Impurities" and in FDA draft guidance for industry: "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches". The TTC is based upon an acceptable excess cancer risk of <1 in 100,000 over lifetime. When also taking into account that the clinical dose regimen consists of 3-5 administrations during a lifetime, the threshold of 120 µg per day can be applied as described in the EU and in the FDA guidance based on extrapolation of the same excess cancer risk to such a short exposure period (concept of staged TTC), therefore the additional risk can be considered to be below 1 in 1 million. For the two impurities [redacted] and [redacted] with higher specification limits, no mutagenic potential was found.

Characterization of decay products in the radioactive drug product

In extended single dose toxicity studies in rats with decayed clinical drug product the decay products were also well tolerated. As the maximum injection volume in patients is 10 mL per person or 0.17 mL/kg, the No Observed Adverse Effect Level (NOAEL) of 1.7 mL/kg represents 10 times the maximum clinical volume based on body weight. At 30 times the clinical volume, only mild transient effects were found, therefore these findings do not indicate any relevant risk for patients. Both tested clinical drug products did not relevantly differ with regard to systemic tolerance.

Conclusions on non-clinical data

In summary, the overall available in vitro and in vivo non-clinical data for florbetaben (^{18}F) do not lead to safety concerns for the use of this agent in patients.

The non-clinical safety pharmacology studies performed with the non-radioactive drug substance [redacted] florbetaben (^{19}F) hydrochloride) showed a favourable safety profile on the nervous system, cardiovascular (including electrocardiography), respiratory and renal function.

There is no need for additional non-clinical data.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

A total of 12 studies were conducted under the Sponsor's florbetaben (^{18}F) clinical development program:

- Two proof-of-mechanism Clinical Phase 1 studies
- The first-in-man proof-of-mechanism investigator-sponsored Melbourne study (A42404)
- The proof-of-mechanism Leipzig study (Study 310863)
- Four additional Clinical Phase 1 studies (Studies 91790, 311722, 312161, and 312043)
- Two supportive Clinical Phase 2 studies (Studies 14311 and 311741)
- One pivotal Clinical Phase 3 study (Study 14595)
- Three non-interventional blinded read studies (no recruitment of patients)
    - One Non-Interventional 'Pooled read study' (Study 16034)
    - New read study: Study FBB-01-01-13
    - Japan read study: Study FBB-01-01-15

It should be noted that specifications of the tracer mass dose changed across the studies. Because global development would require centralized drug production by PET radiopharmacy and wide-spread distribution inevitably results in longer time periods between florbetaben (^{18}F)-radiolabeling, end of synthesis (EoS), and the actual drug administration of the required radioactivity dose of 300 MBq ± 20%, a necessary increase in shelf life required higher radioactivity at EoS. This higher radioactivity resulted in an increase in the specification of the mass dose from ≤ 5 µg / injection in earlier studies to ≤ 50 µg / injection in later studies. This increase came after pre- clinical and clinical data confirmed that neither safety nor efficacy was affected, even at mass doses up to 55 µg / injection. However, the majority of subjects, including those in the later clinical studies, received far lower mass doses than 50 µg / injection. More than 95% of study participants in the safety population were treated with tracer mass dose < 10 µg / injection.

After the approval of Neuraceq in the EU, the MAH conducted a phase IV interventional clinical trial (French Study FBB_01_02_2015), which is not part of the original development program.

Study Title:

Multicenter study to explore the impact of florbetaben (FBB) in change of diagnosis in patients who are evaluated for AD at the CMRR and are eligible for analysis of CSF according to HAS recommendations, and in whom lumbar puncture is contraindicated or CSF results are ambiguous.

Study Description:

Phase 4, multi-center study to explore the clinical utility of FBB in subjects who completed all the workups according to *Haute Autorité de Santé* (HAS) recommendations for Alzheimer's disease (AD), and in whom CSF examination was recommended but lumbar puncture was not feasible for medical reasons or refused by the patients or results of CSF analysis were not contributory.

The primary objective was to estimate the change in the diagnosis after FBB PET imaging (as

documented on eCRF at visit 3). The secondary parameters were:

- Change in level of physician confidence in diagnosis before and after FBB PET scan based on a Physician Diagnostic Confidence Scale;
- The number of subjects with a negative scan and with a positive scan.

The study was completed on 29 Sep 2016. The safety results had no impact on the benefit risk profile of Neuraceq but due to higher number of patients in clinical trials and the subsequent change in the frequency of ADRs, an update of the product information was done. Subjects from this study are included in the numbers given in section SIII.2.

SIII.2 Clinical Trial exposure

Only one indication was used in all clinical trials, therefore only total exposure for all categories have been provided.

A total of 1089 subjects, being considered in the integrated analysis, were enrolled and received either florbetaben (^{18}F) (1077 patients) or Vehicle (12 patients). Due to the fact that in three of the trials the patients received repeated doses according to schedules given in the respective trial protocols, a total number of 1295 florbetaben (^{18}F) exposures were recorded.

The demographic status of the patients is displayed in tables SIII-1 and SIII-2.

Table SIII-1: Patient population (n=1077) by age group and gender

	Females		Males		Total	
	N	%	N	%	N	%
18 - < 40 years	33	5.9	47	9.1	80	7.4
40 - < 65 years	123	21.9	124	24.1	247	22.9
65 - < 80 years	307	54.6	232	45.0	539	50.0
>=80 years	99	17.6	112	21.7	211	19.6
Total	562	100.0	515	100.0	1077	100.0

Table SIII-2: Patient population (n=1077) by ethnic origin

Ethnic origin	N	%
Asian	134	12.4
Black	17	1.6
Caucasian	719	66.8
Other	2	0.2
Unknown	205	19.0
Total	1077	100.0

Special populations

The renal function of the 1077 patients could be assessed by the estimated glomerular filtration rate (eGFR) in the case of 745 out of the 1295 injections. For 550 injections this information is missing.

To indicate ***renal impairment***, eGFR was categorised as follows:

- eGFR <30 mL/min: 5 patient exposures (0.7 % of 745 injections),
- eGFR 30 - <60 mL/min: 149 patient exposures (20.0 % of 745 injections),
- eGFR 60 - <90 mL/min: 372 patient exposures (50.0 % of 745 injections).

A total of 219 (29.4 %) of 745 injections were conducted in patients with a normal eGFR of ≥90 mL/min.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV-2: Exclusion criteria remaining contraindications

Exclusion criteria which remain as contraindications	
Criteria	**Implications for target population**
Hypersensitivity	In predisposed subjects florbetaben (^{18}F) may cause hypersensitivity reactions which can be life-threatening (i.e. anaphylactic reactions).

Table SIV-3: Exclusion criteria not remaining contraindications

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion Criterion**	**Justification for not being a contraindication**
Patients with brain tumour or brain surgery	Structural abnormality may interfere with image interpretation, but amyloid deposition is generally occurring in many regions bilaterally. Thus, a unilateral structural disruption will in most cases not affect the image assessment. There may be cases in which the grey-white matter boundary or structural landmarks are altered in such a way that the image analysis is not possible. This is felt to be a potential confounder in a small number of cases.	In clinical practice, it would be unlikely for a physician to investigate the presence of beta amyloid in patients with a brain tumour. In the case of brain surgery, the efficacy may vary according to the extent of the surgery, however, it is rather likely that this important medical history is known to the physician (if not obvious from the scan itself) – and would be considered in the interpretation of the scan.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Table SIV-1: ADR detection limits

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Not considered to be relevant as a very low dose of drug is used (µg) and no pharmacological effect was expected nor observed.	Not significant.
Due to prolonged exposure	Most subjects received only single dose.	This is in line with the current indication. If patients receive more than one Neuraceq dose, there are typically months or even years between the administrations. This allows Neuraceq to be completely excreted before the next administration. Hence, prolonged exposure is not applicable.
Due to cumulative effects	Repeat doses are only likely to be administered with intervals of several months.	The rather low radiation dose and the single administration make cumulative effects unlikely.
Which have a long latency	There is no scientific evidence that the low radiation dose administered in a single dose would lead to any significant long latency effects.	Not significant.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Children

Florbetaben (18F) is not indicated for use in the paediatric population in the detection of beta-amyloid in the brain, since the pathology does not occur in this age range.

Elderly

69% (603 / 872) of the subjects enrolled in the clinical studies who received florbetaben (^{18}F) are older than 65 years. The mean age in the clinical trials was 68 years. Therefore, there was a high percentage of elderly patients in the clinical study program. The efficacy and safety of florbetaben (^{18}F) has been established in subjects in the age range of 21 to 98 years.

Pregnant or breast-feeding women

Pregnancy: This patient population was not included in the clinical trials, as this would have exposed pregnant women / their foetuses to radiation. Hence, the following statement is included in SmPC section 4.6:

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).

Lactation: This patient population was not to be included in the clinical trials for florbetaben (^{18}F). It is not known if florbetaben (^{18}F) is excreted in human milk. Therefore, the following statement is included in SmPC section 4.6:

Breast-feeding

It is not known 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.

Patients with hepatic impairment
No targeted studies have been performed in patients with hepatic disorders. However, it should be noted that florbetaben (^{18}F) is metabolized by several Cytochrome P450 (CYP) enzymes that are not exclusively expressed in the liver but also present in other organs. Thus, in the case of hepatic impairment in the metabolic capacity, a compensatory extrahepatic metabolic capacity may be present.

Furthermore, as florbetaben (^{18}F) is applied as a single low microdose, i.e. pharmaco-dynamically inactive dose, a clinically relevant effect with respect to safety and efficacy is not expected in patients with hepatic impairment. Available data do not suggest a need for a dose adjustment of florbetaben (^{18}F) in patients with mild or moderate reduction in liver function.

Florbetaben (^{18}F) is not recommended in patients with severe hepatic impairment. SmPC section 4.4 states:

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 (18F) is excreted primarily through the hepatobiliary system and patients with hepatic impairment have the potential of increased radiation exposure (see section 4.2).

Section 4.2 states:

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.

Patients with renal impairment

No targeted studies have been performed in patients with renal disorders. However, in patients with renal impairment, efficacy and safety of florbetaben (^{18}F) was not different compared to patients with normal renal function.

The pooled analysis of all Phase I – III data included 406 AD subjects and 291 non- demented volunteers (≥55 years). In the group of AD subjects, 8% had normal renal function; 35% had mild renal impairment, 19% moderate renal impairment and 1% had severe renal impairment (missing data: 38%). The respective percentages in the group of non-demented volunteers were 24%, 51%, 14% and <1%, respectively (missing data: 11%). The pooled analysis of subjects showed no relevant effect of renal function on the safety of florbetaben (^{18}F).

Further analysis of the influence of renal impairment on efficacy was evaluated as part of the Phase II program. In a total of 387 subjects (198 ADs and 189 healthy volunteers (HVs)), an analysis of covariance model that assessed for effects of renal impairment (as reflected by Creatinine Clearance and age) on florbetaben (^{18}F) visual and quantitative PET scan results was performed. The model did not detect differences in visual or quantitative scan results in subjects with renal impairment when compared to the entire phase 2 cohort. In subjects with renal impairment efficacy and safety of florbetaben (^{18}F) was not different compared to subjects with normal renal function. Subjects with reductions in renal function do therefore not require dose reduction.

See also above (section on patients with hepatic impairment) on SmPC stipulations for patients with renal impairment.

Patients with cardiovascular impairment

No targeted studies in the development program have been performed in patients with cardiovascular impairment. However, cardiovascular diseases are common co-morbidities in patients with dementia [16].

Study 311741 part A, a Phase 2 open-label, non-randomized was comprised of 150 subjects (69 HVs and 81 AD patients), included ECG recordings during the safety evaluation. As a reflection of the frequent cardiovascular co-morbidity observed in the elderly populations involved, 53.6% of HVs and 51.9% of ADs had abnormal ECG findings at baseline. No significant effects of florbetaben administration on heart rate, RR interval, PQ interval, QRS duration, QT interval and QTc intervals (according to Bazett and Fridericia) were detected. No trends in changes from baseline indicative of a safety concern were observed for any of the measured ECG parameters.

Florbetaben (^{18}F) is currently being developed for a cardiac amyloidosis indication and has been utilized in patients with suspected or confirmed cardiac amyloidosis in eight investigator sponsored clinical trials with a total of 228 patients. No serious adverse events have been reported in these studies.

Immunocompromised patients

No targeted studies in the development program have been performed in immune-compromised patients.

Patients with other relevant co-morbidity
Not applicable

Patients with other relevant co-morbidity
Not applicable

Patients with a disease severity different from inclusion criteria in clinical trial population
Not applicable

Sub-populations carrying known and relevant polymorphisms
Not applicable

Patients of different racial and/or ethnic origin
The pharmacokinetics of florbetaben (^{18}F) in Japanese volunteers was investigated in Study 91790 and the results compared to those in a very similar study in Caucasian volunteers (Study 311722). No significant differences between Caucasian and Japanese subjects were observed with respect to the pharmacokinetics of total radioactivity and florbetaben (^{18}F) or in the metabolite profile.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Due to the special properties of Neuraceq (short half-life), the product is only produced on demand. Patient exposure can be easily calculated from amount of product delivered, as one dose is applied per patient.

SV.1.2 Exposure

Cumulatively, [redacted] patients have received commercial Neuraceq as of 20 Feb 2023:

- [redacted] in the European Union,
- [redacted] in the UK,
- [redacted] in the US,
- [redacted] in Canada,
- [redacted] in Asia Pacific (Japan, South Korea, Taiwan and Australia) and
- [redacted] in South America (Brazil, Chile).

Of note, these dose numbers do not include doses delivered to studies investigating the effect of Disease Modifying Drugs or other clinical studies.

A table, as suggested by the template is not applicable, as no data for additional stratification (beyond geographical stratification reported above) are available.

SV.2 Potential for off-label use

The marketing authorization holder has received three literature reports on off-label use from the post-marketing setting and one compassionate use report on off label use. The potential for off-label use is considered limited, given the small number of case reports compared to the exposure.

Furthermore, Neuraceq has been evaluated in clinical studies investigating the following populations:

Cognitively normal subjects: Florbetaben (^{18}F) is only indicated for use in a population which already has a decrement in cognitive function and will support diagnosis in the context of clinical signs and symptoms (including cognitive impairment). As a consequence, use is rather unlikely in cognitively normal subjects. No further risk minimisations activities are currently considered necessary.

Multiple sclerosis (MS): Although β-amyloid protein is mainly linked to AD, a connection between β-amyloid protein and MS is suggested. Amyloid precursor protein (APP) is extensively expressed in humans. Although information on APP proteolytic processing in MS is scarce, we currently know that it is upregulated in damaged axons, which suggests that it may have a protective effect in MS and constitute a reliable marker. Several mechanisms associated with this increased expression may affect the degree of remyelination in MS. According to Matías-Guiu et al.(2016) [17] amyloid-PET may serve as a tool for determining the degree of demyelination and remyelination as well as a means of studying molecular changes linked to remyelination in MS in vivo. To date, no further risk minimisations activities are considered necessary.

[redacted] A pilot study to determine the feasibility of florbetaben (^{18}F) PET in diagnosing [redacted], and correlate with [redacted] in 14 subjects was performed. [redacted] conclude florbetaben (^{18}F) PET imaging may be useful in the accurate diagnosis and differentiation of [redacted] florbetaben (^{18}F) retention index is an independent determinant of [redacted] Further development and publications are monitored closely. No further risk minimisations activities are considered necessary at the moment.

Systemic amyloidosis: This corresponds to a variety of conditions in which amyloid proteins are abnormally deposited in organs and/or tissues. It is a rare disease with an incidence of 1 in 100.000 mainly affecting elderly people at the age of 65. The diagnosis of amyloidosis can be difficult by standard procedures and, therefore, patients could potentially be dosed with florbetaben (^{18}F) and a whole-body PET preformed. No data exist at present on this use. However, considering that the patient population is small and the fact that systemic amyloidosis is part of the differential diagnosis possibilities for AD, the potential risk is negligible. No further risk minimisations activities are considered necessary at the moment.

Down's syndrome: Since beta-amyloid deposition is also linked to Down's syndrome in adult life, florbetaben (^{18}F) might be used in this population for diagnostic purposes. This is subject

of clinical research and the first controlled study experiences have already been obtained. No further risk minimisation activities seem currently necessary.

Human immunodeficiency virus (HIV) – associated neurocognitive disorder (HAND): HAND is found in 30%–50% of individuals with HIV infection. To date, no HIV positive individual has been reported to have a positive amyloid PET scan. Turner et al. (2016) [19] reported about a 71-year-old HIV positive individual with HAND. This case report suggests that progressive dementia in older HIV positive individuals may be due to HAND, AD, or both. HIV infection does not preclude CNS amyloid deposition. Amyloid PET imaging may be of value in distinguishing HAND from AD pathologies.

Given the clearly labelled indication, use of florbetaben (^{18}F) for a medical purpose not in congruence with the stipulations of the registration might occur within studies (rather than in single experiences). Further development and publications are monitored closely.

No additional risk minimisation activities are considered necessary.

Potential for paediatric off-label use

The safety and efficacy of florbetaben (^{18}F) have not been established in the paediatric population because this drug is not indicated for use in the paediatric population in the detection of beta-amyloid in the brain since the pathology is not known to occur in this age range. It is highly unlikely that florbetaben (^{18}F) will be used in the paediatric population.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The substance florbetaben (18F) is not known to hold abuse potential. Due to the special properties of Neuraceq (short half-life), the product is only manufactured on demand in response to prescription, and distribution is highly controlled owing to its radioactive nature. In addition, the product is delivered directly to hospitals and administered by professionals in a clinical setting in a highly controlled environment.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable, as the initial RMP submission occurred before current guidance necessitated this chapter.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable, as the initial RMP submission occurred before current guidance necessitated this chapter.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable, as the initial RMP submission occurred before current guidance necessitated this chapter.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

With RMP version 6.0 and as proposed during the assessment of the type II variation to submit the PASS2 clinical study report (procedure number: EMEA(H/C/002553/II/0033), "Injection site pain", "Injection site irritation", "hypersensitivity", "injection site extravasation", "Reactions due to ethanol content of the formulation, "Off-label use in persons with Down's syndrome and children", "Safety in patients with hepatic or renal impairment" and "Drug-drug interactions with disulfiram" are deleted from the summary of safety concerns.

With RMP version 7.0 and as proposed during the assessment of the procedure number: EMA/VR/0000227744, "PET scan interpretation error" deleted from the summary of safety concerns.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks: Not applicable.

Important Potential Risks: Not applicable.

SVII.3.2. Presentation of missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include adverse reaction management, signal management, and other routine PV activities as per GVP.

III.2 Additional pharmacovigilance activities

No additional PV activities proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

Not applicable, as no safety concerns are in place anymore.

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

Not applicable

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Neuraceq (florbetaben (^{18}F))

This is a summary of the risk management plan (RMP) for Neuraceq. The RMP details important risks of Neuraceq, how these risks can be minimised, and how more information will be obtained about Neuraceq's risks and uncertainties (missing information).

Neuraceq's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Neuraceq should be used.

This summary of the RMP for Neuraceq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Neuraceq's RMP.

I. The medicine and what it is used for

Neuraceq is authorised 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. (see SmPC for the full indication). It contains florbetaben (^{18}F) as the active substance and it is given by intravenous injection.

Further information about the evaluation of Neuraceq's benefits can be found in Neuraceq's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage Neuraceq | European Medicines Agency (EMA) (europa.eu).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Neuraceq, together with measures to minimise such risks and the proposed studies for learning more about Neuraceq's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Neuraceq are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Neuraceq. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Neuraceq.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Neuraceq.

Part VII: Annexes

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted] [redacted] [redacted]	[redacted]	[redacted]	[redacted] [redacted]
[redacted] [redacted] [redacted]	[redacted]	[redacted]	[redacted] 2020 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Not applicable.

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

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