EU RISK MANAGEMENT PLAN FOR VIZAMYL (Flutemetamol (^{18}F))

RMP version to be assessed as part of this application:

RMP Version number:	6.0
Data lock point for this RMP:	30 September 2025
Date of final sign off:	November 2025
Rationale for submitting an updated RMP:	Following PSUSA00010293202410, PRAC requested updating the RMP to remove the important potential risk "PET imaging interpretation errors" as it is considered an efficacy issue, not a safety issue. PRAC also requested removal of educational material as an additional risk minimisation measure.
Summary of significant changes in this RMP:	– Removed "PET imaging interpretation errors" from safety specification. – Removed educational material and follow-up questionnaire. – Updated Module SI with recent literature. – Revised section SVII.1.1. per Module XVI Addendum I (embryo-foetal risk minimisation). – Minor edits to exposure sections, language, and spelling.
Other RMP versions under evaluation:	None
Details of the currently approved RMP:	
Version number:	5.0
Approved with procedure:	PSUSA/00010293/202410
Date of approval (opinion date):	05 June 2025

QPPV Name: Burkhard Roessink (MD)

[redacted]

QPPV/Deputy QPPV Signature:

TABLE OF CONTENT

PART I: PRODUCT OVERVIEW

Active substance(s) (INN or common name)	Flutemetamol (^{18}F), [^{18}F]flutemetamol
Pharmacotherapeutic group(s) (ATC Code)	Other central nervous system diagnostic radiopharmaceuticals, ATC code: V09AX04
Marketing Authorisation Holder	GE Healthcare AS
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Vizamyl 400 MBq/mL solution for injection (Vizamyl)
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** – The active drug substance of Vizamyl, flutemetamol (^{18}F), is structurally similar to thioflavin-T, a dye that is used to stain amyloid in neuro-histological procedures. – *In vitro* studies have indicated that flutemetamol (^{18}F) binds selectively to amyloid-β neuritic plaques in the brain. – 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.
	Summary of mode of action – Vizamyl is a fluorine-18 labelled positron emission tomography (PET) diagnostic agent for visual detection of fibrillar amyloid-β in the brain. – Flutemetamol (^{18}F) binds to β-amyloid neuritic plaques in the brain. – *In vivo*, flutemetamol (^{18}F) is also able to detect β-amyloid diffuse plaques when they are frequent, by PET imaging.
	Important information about its composition Not applicable.
Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/Vizamyl-epar-product-information_en.pdf
Indication(s) in the EEA	**Current:** – This medicinal product is for diagnostic use only. – Vizamyl 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 Alzheimer's disease (AD) and other causes of cognitive impairment. Vizamyl 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.
	Proposed: N/A
Dosage in the EEA	**Current:** – The recommended activity for Vizamyl is 185 MBq administered intravenously (as a bolus within approximately 40 seconds). – The volume of the injection should not be less than 1 mL and not exceed 10 mL.

	Proposed: N/A
Pharmaceutical form(s) and strengths	**Current:** – Solution for injection. – Each mL of solution for injection contains 400 MBq of flutemetamol (^{18}F) at reference date and time. The activity per vial may range from 400 MBq to 4000 MBq or from 400 MBq to 6000 MBq at the reference date and time.
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

Mild cognitive impairment (MCI), amnestic mild cognitive impairment (aMCI), possible Alzheimer's dementia and Alzheimer's Disease (AD)

Dementia is a clinical syndrome characterised by a decline in mental ability severe enough to interfere with daily life. Alzheimer's disease (AD) is the most common cause of dementia. It is a progressive disease, and affected individuals eventually require full support to complete simple daily tasks. Alzheimer's dementia, marked by significant cognitive decline that interferes with daily functioning, is preceded by a condition called mild cognitive impairment (MCI), which involves less severe loss of memory and/or reasoning skills, and in contrast to the dementia stage does not involve functional impairment. MCI that primarily affects memory is known as "amnestic MCI" (aMCI).

Previously a definite diagnosis of AD was based on 3 criteria: the presence of dementia and the presence of two abnormal proteins in the brain (amyloid and tau). Prior to the last few decades, brain amyloid and tau could only be detected through post-mortem examination of brain tissue. Only in the last few decades, have positron emission tomography (PET) imaging agents been developed to visualize amyloid deposits in living patients. In 2024, a PET imaging agent for visualizing tau was also approved.

AD is currently regarded as a biological continuum, integrating clinical symptoms with biomarker evidence. According to the 2024 revised criteria from the Alzheimer's Association and the National Institute on Aging, diagnosis requires validated biomarkers, such as amyloid and tau detected via cerebrospinal fluid (CSF), PET, or plasma, in symptomatic individuals. These biomarkers support diagnosis but are not recommended for screening cognitively normal individuals outside research settings [Hansson et al. 2022]. Clinical diagnosis alone has limitations, with misdiagnosis rates as high as 20–30%, underscoring the importance of biomarker confirmation for accurate assessment [Gaugler et al. 2013].

In 2024 the International Working Group (IWG) updated their recommended diagnostic criteria for AD [Dubois et al. 2024]. The IWG proposes three distinct categories to describe individuals across the AD continuum, emphasizing both clinical status and biomarker profiles: 1) Asymptomatic At-Risk for AD, 2) Presymptomatic AD, and 3) AD [Dubois et al. 2024].

Asymptomatic At-Risk for AD refers to cognitively normal individuals who show biomarker signs of brain amyloidosis (with or without limited tauopathy), indicating an increased, but not certain, risk of future cognitive decline. These individuals should not be diagnosed with AD.

Presymptomatic AD describes cognitively normal individuals with biomarker or genetic profiles that predict a very high lifetime risk of developing AD. This includes carriers of autosomal dominant mutations (APP, PSEN1, PSEN2), individuals with Down syndrome, APOE ε4 homozygotes with SORL1 loss-of-function, and those with both amyloid and neocortical tau PET positivity.

According to IWG AD is diagnosed in individuals presenting with cognitive impairment accompanied by biomarker evidence of AD pathology, as confirmed through CSF analysis or PET imaging. It includes both prodromal (mild cognitive impairment) and dementia stages,

with clinical presentations ranging from typical memory loss to atypical variants like logopenic aphasia or cortico-basal syndrome.

The National Institute on Aging and the Alzheimer's Association (NIA-AA) Workgroup also published revised criteria for diagnosis and staging of AD in 2024 [Jack et al. 2024]. The NIA-AA defines AD as a biological continuum that begins with the presence of Alzheimer's neuropathologic change (ADNPC), even in asymptomatic individuals. As the pathological burden increases, clinical symptoms emerge and progress. This marks a shift from a syndromic to a biologically anchored definition of AD.

Core 1 biomarkers, including amyloid PET, CSF markers, and plasma biomarkers like phosphorylated tau 217, are considered sufficient to diagnose AD biologically [Jack et al. 2024]. These biomarkers reflect the presence of both amyloid plaques and tau tangles. Core 2 biomarkers, such as tau PET and neurodegeneration-related biofluid markers, typically change later in the disease course, providing prognostic information and strengthen diagnostic confidence when symptoms are present [Jack et al. 2024].

The framework also introduces an integrated biological and clinical staging system, acknowledging that factors like cognitive reserve, resistance, and co-pathologies can influence the relationship between biological markers and clinical symptoms. This approach aims to bridge research and clinical care by aligning diagnosis and staging with underlying pathology rather than clinical presentation alone.

The NIA-AA and IWG criteria differ in how they define and diagnose AD. The NIA-AA views AD as a biological continuum that begins with neuropathologic changes detectable by biomarkers, even before symptoms appear; an abnormal Core 1 biomarker (e.g., amyloid PET, CSF, plasma p-tau 217) is sufficient for diagnosis. In contrast, the IWG requires both cognitive impairment and biomarker evidence to diagnose AD, emphasizing that asymptomatic individuals, even with positive biomarkers, should not be labelled as having the disease. While NIA-AA promotes early biological diagnosis and staging, IWG focuses on clinical relevance and stratifies individuals into "at-risk", "presymptomatic", and "Alzheimer's disease" categories based on biomarker profiles and symptoms.

Vizamyl (Flutemetamol ^{18}F Injection) is a PET amyloid imaging agent indicated for use in adults with cognitive impairment (MCI, aMCI or dementia), for whom the physician would like to exclude or confirm the presence of brain amyloid, which would thus exclude or support AD as likely underlying cause to support or exclude a diagnosis of prodromal AD (MCI due to AD) or Alzheimer's dementia.

Although Vizamyl is primarily utilized to exclude AD in patients lacking amyloid deposition, its clinical significance has grown substantially following the regulatory approval of disease-modifying therapies in both the United States and the European Union.

Amyloid and Risk of Progression from MCI to Dementia

Research has shown that patients with MCI who are amyloid-positive, identified through CSF biomarkers or amyloid PET imaging, have a significantly higher risk of progressing to Alzheimer's dementia. A systematic review and meta-analysis [Huszár et al. 2024] of 36 cohorts involving 7793 participants, showed that individuals with amyloid pathology have a significantly increased risk (5.18-fold) of progressing from normal cognition to MCI or dementia, with the risk rising to 11.6-fold when both amyloid and tau pathologies are present,

underscoring the predictive value of combined biomarkers in identifying those at highest risk for AD.

[Dickerson and Wolk. 2013] demonstrated that CSF amyloid-β levels, especially when combined with tau markers and neuroimaging features like hippocampal volume, provide strong predictive value for progression. Their findings support the idea that amyloid and neurodegeneration markers offer complementary prognostic information. It was further confirmed by [van Maurik et al. 2019] that amyloid PET imaging adds substantial value in individualized risk prediction. Their longitudinal studies showed that amyloid-positive MCI patients had significantly faster cognitive decline and higher conversion rates to Alzheimer's dementia. The combination of amyloid burden and cognitive performance allowed for more accurate stratification of progression risk, supporting the use of amyloid PET in clinical decision-making.

A 7-year prospective study from the Harvard Aging Brain Study [Hanseeuw et al. 2019] assessed 60 cognitively normal older adults using repeated PET imaging to track amyloid-β and tau accumulation. It found that an initial rise in amyloid-β was associated with subsequent tau increases, which in turn predicted cognitive decline. Participants with higher amyloid and greater tau accumulation were more likely to progress to mild cognitive impairment, highlighting a sequential pathophysiological cascade from amyloid to tau to cognitive symptoms in preclinical AD.

[Wolk et al. 2018] evaluated whether flutemetamol (^{18}F) PET imaging and other biomarkers could predict progression from aMCI to probable AD in a multicentre cohort study. Among 232 patients with aMCI, those with positive amyloid PET scans had a significantly higher rate of progression to AD over 36 months (53.6%) compared to those with negative scans (22.8%). The risk increased further when low hippocampal volume and poorer cognitive status were present, with hazard ratios rising to 5.60 and 8.45, respectively. The findings support the use of combined biomarkers to more accurately assess the likelihood of clinical progression in aMCI patients.

Incidence

AD is a leading cause of dementia worldwide, with its incidence and prevalence increasing due to aging populations. Globally, over 57 million people were living with dementia in 2019, and this number is projected to reach 152 million by 2050 [Global Burden of Disease Study. 2022]. An estimated 7.2 million Americans aged 65 and older are living with Alzheimer's dementia in 2025, with expectations that this figure will nearly double by 2050 [Alzheimer's Association. 2025].

Recent studies suggest that the incidence rate of AD and other dementias has declined in recent decades, likely due to improvements in modifiable risk factors such as better management of hypertension and increased educational attainment [Alzheimer's Association. 2025]. Despite this decline, the overall number and proportion of Americans affected is expected to rise, due to the aging population, and the number of people over 65 and particularly those aged 85 and older. Age-specific incidence rates show that approximately 0.4% (4 per 1000) of individuals aged 65–74 develop AD annually, increasing to 3.2% (32 per 1000) for ages 75–84, and 7.6% (76 per 1000) for those aged 85 and older. As a result, the annual number of new cases is projected to double by 2050 [Alzheimer's Association. 2025].

In Europe, incidence rates are comparable to those in North America. An analysis was performed in aggregated data from individuals >65 years of age in 7 population-based cohort studies in the United States and Europe from the Alzheimer Cohort Consortium [Wolters et al. 2020]. The study comprised more than 49000 individuals whereof 8.6% developed dementia. The incidence rate of dementia increased with age, similarly for women and men, ranging from about 0.4% (4 per 1000 person-years) in individuals aged 65–69 years to 6.5% (65 per 1,000 person-years) for those aged 85–89 years. The study showed that incidence rate of dementia declined by 13% per calendar decade consistently across studies [Wolters et al. 2020].

Globally, the disability-adjusted life years (DALYs) among those aged 65 and older linked to dementia grew by 176% between 1990 and 2021, from 11.8 million to 32.6 million [Liu et al. 2025]. The global burden of dementia is increasing, with a more pronounced trend in high socio-demographic index (SDI) regions, particularly among the elderly population [Liu et al. 2025]. Between 1990 and 2021, the age-standardized DALYs for dementia among the population aged 65 and older increased in all five SDI regions, particularly in countries with low SDI. Excluding the high SDI region, the age-standardized mortality rate for dementia among individuals aged 65 and older has shown an increase each year. This trend has been more noticeable in nations with low SDI. In terms of mortality and DALYs, the global burden of dementia has remained stable over the past 32 years, except for the low-middle SDI and low SDI regions.

Prevalence

The prevalence among those over the age of 60 varies by region, with Southeast Asia reporting a prevalence of 2.9%, Europe at 6.5%, and other regions experiencing rates between 3.1% and 5.7% [World Health Organization. 2022].

The prevalence among Americans aged 65 and older is about 1 in 9, or 11%, with nearly two-thirds of those affected being women [Alzheimer’s Association. 2025].

In 2019 about 14 million people (one in 11 of those aged 65 years and older) were living with dementia in the European region, and the prevalence was expected to double by 2030 [WHO Regional Office for Europe. 2025]. Among people aged 65 years or older in 2019, the prevalence was 8.46% or roughly one in 11 people. The number of dementia-related DALYs rose from 3.7 million in 2000 to 7.8 million in 2021 in the European region, with twice as many for women than for men.

Demographics of the target population in the authorized indication – age, gender and risk factors for the disease

Demographics

Dementia, including AD, primarily affects individuals over the age of 60, with prevalence increasing significantly with age. Women are disproportionately affected, making up nearly two-thirds of Americans with AD and more than half of those living with dementia in Europe [Alzheimer Europe. 2019, Alzheimer’s Association. 2025]. Age remains the strongest risk factor: in Europe, prevalence rises from 0.6% among 60–64-year-olds to 21.9% in those aged

85–89, while in the U.S., 5.15% of people aged 65–74 have AD compared to 33.4% of those 85 and older [Alzheimer Europe. 2019, Alzheimer's Association. 2025].

In the U.S. the risk of AD and other dementias varies by race and ethnicity with non-Hispanic Black and Hispanic older adults showing higher prevalence rates than non-Hispanic Whites, 19% and 14% respectively, compared to 10% [Alzheimer's Association. 2025].

Risk factors

As noted above, age and female sex are risk factors for dementia and AD. Genetics may also play a role in some cases if there is a family history of AD or if the patient is a carrier of 1 or 2 alleles of the APOE-4 gene) [Alzheimer's Association. 2018].

Other risk factors include vascular disease (cerebrovascular and cardiovascular disease, hypertension), metabolic diseases (overweight, obesity, diabetes), life style factors (smoking, heavy alcohol consumption), dietary factors (high consumption of saturated fat, vitamin B deficiencies), and other factors including depression and traumatic brain injury [Winblad et al. 2016]. Protective factors include high education and socioeconomic status, physical activity, a diet rich in polyunsaturated fats and vitamins, and drugs (antihypertensive, statins, hormone replacement therapy, non-steroidal anti-inflammatory drugs (NSAIDS)) [Winblad et al. 2016].

According to the 2024 update to the standing "Lancet Commission in Dementia Prevention" [Livingston et al. 2024] two new modifiable risk factors for dementia (vision loss and high cholesterol) were added to the 12 risk factors identified by the 2020 Lancet Commission (i.e., less education, head injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, infrequent social contact, and air pollution). Key individual interventions to enable risk reduction to prevent or delay dementia include preventing and treating hearing loss, treating vision loss and depression, cognitive stimulation throughout life, decreasing smoking, reducing and treating vascular risk factors (i.e., cholesterol, diabetes, obesity, and blood pressure), reducing head injury, and maintaining and encouraging physical activity.

The main existing treatment options

Symptomatic Treatments

Symptomatic treatments for AD aim to temporarily alleviate cognitive and behavioural symptoms without altering the underlying disease progression. The most prescribed drugs are cholinesterase inhibitors, including donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne), which work by preventing the breakdown of acetylcholine, a neurotransmitter important for memory and learning. These medications are typically used in mild to moderate stages of the disease and may provide modest improvements in cognition and daily functioning. For moderate to severe AD, memantine (Namenda), an N-Methyl-D-Aspartate (NMDA) receptor antagonist, is often prescribed to regulate glutamate activity and reduce symptoms such as agitation and confusion. Combination therapy with memantine and donepezil is also available. [Alzheimer's Association. 2025]

On May 11, 2023, the U.S. Food and Drug Administration (FDA) approved brexpiprazole (Rexulti) oral tablets for the treatment of agitation associated with dementia due to AD [U.S.

FDA. 2023]. This marks the first FDA-approved treatment specifically for this behavioural symptom.

Disease-Modifying Therapies

Recent advances have led to the approval of disease-modifying therapies that target the underlying pathology of AD. Leqembi (lecanemab) and Kisunla (donanemab) are monoclonal antibodies that target beta-amyloid plaques in the brain. These drugs are approved for use in early-stage AD or MCI and have shown modest slowing of cognitive decline in clinical trials. Both treatments require confirmation of amyloid pathology via PET scan or CSF analysis and carry risks such as amyloid-related imaging abnormalities (ARIA), including brain swelling and microbleeds [Being Patient. 2025, National Institute on Aging. 2023, U.S. FDA. 2024]. These therapies represent a shift toward targeting the biological mechanisms of AD and are considered a foundation for future combination and precision medicine approaches.

Natural history of the indicated condition in the population, including mortality and morbidity

AD is a progressive neurodegenerative disorder that typically begins with subtle memory loss and advances to severe cognitive and functional impairment. The disease course spans several years, often beginning with a preclinical phase where neuropathological changes (amyloid plaques and tau tangles) accumulate silently. This is followed by MCI, particularly of the amnestic type, and eventually progresses to dementia, where daily functioning is significantly impaired.

The average duration from diagnosis to death ranges from 4 to 8 years, though some individuals may live up to 20 years post-diagnosis. Morbidity is substantial, with patients experiencing progressive loss of memory, reasoning, language, and independence. Behavioural and psychological symptoms such as depression, agitation, and psychosis are common, further complicating care and quality of life.

Mortality associated with AD has increased significantly over the past two decades. In the U.S there were over 120000 deaths due to AD in 2022. Between 2000 and 2022, reported deaths from AD rose by more than 140%, while deaths from other major diseases declined. Globally, dementia-related deaths reached an estimated 1.55 million in 2019 [Alzheimer's Association. 2025].

AD and other dementias were the 7th leading cause of death in 2021 according to the WHO [World Health Organization. 2024]. Before COVID-19 became the third-leading cause of death in 2020, AD was the sixth-leading cause of death; preliminary data for 2023 indicates that AD will once again be the sixth-leading cause of death [Alzheimer's Association. 2025]. It is also a leading cause of disability and poor health (morbidity) in older adults, and a person with AD are likely to live through years of morbidity as the disease progresses.

The number of deaths from dementia of any type is much higher than the number of reported AD deaths. In 2022, some form of dementia was the officially recorded underlying cause of death for 292881 individuals (this includes the 120122 from AD) in the U.S.

Severe dementia frequently causes complications such as immobility, swallowing disorders and malnutrition that significantly increase the risk of acute conditions that can cause death.

One such condition is pneumonia (infection of the lungs), which is the most commonly identified immediate cause of death among older adults with AD or other dementias.

Dementia is the leading cause of disability and dependency in older adults, affecting almost 8 million people in the European Union [Alzheimer Europe. 2019]. Typical symptoms of dementia include memory loss and disorientation, as well as problems with thinking, mood and practical activities in daily life. These symptoms are usually relatively mild in the early stages but gradually get worse as dementia progresses.

AD is also associated with high rates of comorbid conditions, including cardiovascular disease, diabetes, and stroke, which further complicate care and increase health risks. Studies show that people with Alzheimer's dementia have double the five-year mortality rate compared to age-matched individuals without dementia (115 vs. 60.6 deaths per 1,000 person-years; approximately 11.5% vs. 6.06%). Additionally, the disease imposes a heavy burden on caregivers and healthcare systems, with nearly half of long-term care patients in the U.S. diagnosed with dementia and high utilization of services such as hospice and residential care [Alzheimer's Association. 2025].

As described above patients with MCI who are amyloid-positive, identified through CSF biomarkers or amyloid PET imaging, have a significantly higher risk of progressing to AD. It should be noted that it is difficult to determine how many deaths are caused by AD each year because of the way causes of death are recorded, and the vast majority of death certificates listing AD as an underlying cause of death are not verified by autopsy.

Important co-morbidities

Several comorbidities may be seen in patients being evaluated for AD. As the rate of all types of dementia (as well as MCI, aMCI and AD) tend to increase with age, chronic medical conditions associated with age, especially cardiovascular disease and cancer, may be seen in persons with dementing illness. Several conditions are more prevalent in dementia than the general population, even after controlling for age effects. These include behavioural and psychological symptoms such as depression and apathy. Vascular disease (cerebrovascular and cardiovascular) and thyroid disease are also common in dementia.

The target populations for Vizamyl are likely to be on multiple medications due to common comorbidities, however, drug interactions with Vizamyl are considered extremely unlikely due to the rapid clearance of Vizamyl from the circulation after intravenous administration.

Module SII - Non-clinical part of the safety specification

No safety concerns regarding Vizamyl/ flutemetamol (^{18}F) have been identified from studies concerning safety pharmacology, pharmacodynamic drug interactions with anti-amyloid therapies, single and repeat dose toxicity, reproductive toxicity, local tolerance and radiation dosimetry. These non-clinical studies support the safety of the product for the intended use.

Non-clinical studies suggest a high safety margin regarding influence of flutemetamol (^{18}F) on QT interval. *In vitro* studies suggested a genotoxic potential of flutemetamol (^{18}F), but this has not been confirmed in subsequent in vivo studies. Table 1 presents a summary of the findings from non-clinical studies. Additional non-clinical studies are not planned for the medicinal product.

Table 1 Significant safety findings for flutemetamol (^{18}F) from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity	
Reproductive toxicity / Developmental toxicity Reproductive or developmental toxicity studies have not been carried out, as Vizamyl is a diagnostic radiopharmaceutical imaging agent intended for infrequent administration with significant intervals between injections. Potential adverse effects on fertility have been assessed by an evaluation of the male and female reproductive organs in repeated dose toxicity studies in rodents (rats) and non-rodents (dogs), which showed that there were no adverse treatment-related effects on fertility. Results from bio-distribution studies with the radiolabelled test item flutemetamol (^{18}F) was used to calculate radiation dosimetry to estimate exposure of the gonads, and to perform a risk assessment of possible adverse effects on fertility. The cumulated exposure to the gonads following administration of Flutemetamol (^{18}F) Injection was calculated to be 0.008 μSv/MBq. These values are in line with what has been observed for other diagnostic radiopharmaceuticals and are considered to represent an acceptable risk. No embryonic, foetal or perinatal toxicity studies have been conducted as pregnancy and breast feeding are contraindicated for this class of imaging agents, and both pregnancy and breast feeding are exclusion criteria in clinical trials.	There is no reason to suspect any safety concerns regarding the genotoxic potential of Vizamyl/ flutemetamol (^{18}F). Vizamyl had no effect on male and female reproductive organs in repeated dose toxicity studies. The lack of reproductive/developmental toxicity studies is justified because Vizamyl is intended for use in elderly patients and not is not intended for use in women of childbearing age. The likelihood of flutemetamol (^{18}F) being used in pregnant or breast-feeding mothers is expected to be unlikely or very low. The summary of product characteristics (SmPC) states that flutemetamol (^{18}F) should not be given during pregnancy unless clearly necessary.
Genotoxicity An overall assessment of genetic toxicology indicates that although flutemetamol (^{18}F), or more likely one or more of its metabolites, have shown genotoxic potential *in vitro*, this does not represent an *in vivo* risk. No evidence of genotoxicity was observed in three different *in vivo* assays evaluating the bone marrow and liver after exposure of up to 75 times the recommended mean mass dose of 20 μg flutemetamol (^{18}F). The genotoxic potential of flutemetamol (^{18}F) has been thoroughly investigated in a comprehensive set of studies consisting of a reverse mutation assay in *Salmonella typhimurium* (Ames test), a mouse lymphoma assay (MLA), two *in vivo* micronucleus (MN) assays in the bone marrow and a further *in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. The flutemetamol (^{18}F) -related impurities have not been directly evaluated for genotoxicity, however, *in*	No cause for safety concerns regarding the genotoxic potential of Vizamyl/ flutemetamol (^{18}F). Furthermore, the specified limit of flutemetamol (^{18}F) and related impurities is 2 μg/mL or a maximum of 20 μg/10 mL-dose, which is significantly lower than the dosage used in the toxicity studies.

Table 1 Significant safety findings for flutemetamol (^{18}F) from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
silico assessment of the five main flutemetamol (^{18}F) - related impurities predicted that since these impurities are similar in structure, they probably share common genotoxic pathways. Of these impurities, only one has been detected at a significant level (0.15 µg/mL or 1.5 µg assuming a maximal 10 mL-dose). This unspecified impurity was observed at a significant level in only one of the 80 test batches (1%) and at a low level of 0.49 µg/ml. The *in vivo* genotoxic evaluation of flutemetamol (^{18}F) is therefore applicable for flutemetamol (^{18}F) and related impurities indicating that the genotoxic risk associated with the administration of Flutemetamol (^{18}F) Injection is very low.	
Carcinogenicity Carcinogenicity studies have not been conducted, since Vizamyl is a diagnostic imaging agent intended for infrequent administration with significant intervals between injections. There is no evidence of pre-neoplastic lesions in repeated dose toxicity studies in animals (rats and dogs) and no long-term retention of parent compound or metabolite(s) resulting in local tissue reactions or other pathophysiological responses.	No cause for safety concerns regarding the carcinogenic potential of Vizamyl/ flutemetamol (^{18}F). The lack of carcinogenicity toxicity studies is justified because flutemetamol (^{18}F) is administered infrequently, and there is no evidence of in vivo genotoxicity or any pre-neoplastic changes due to repeated doses.
Safety pharmacology There were no safety concerns from studies concerning safety pharmacology.	

Module SIII - Clinical trial exposure

The cumulative numbers of subjects exposed to the investigational medicinal product (Flutemetamol (^{18}F) Injection), to placebo, and/or to active comparator(s) from completed clinical trials since the development international birth date (DIBD), 9 October 2007, are presented in this module.

Exposure in GE Healthcare sponsored studies

Overall, 831 subjects (259 healthy volunteers and 572 patients) were dosed with Flutemetamol (^{18}F) Injection in the clinical development program of GE Healthcare sponsored studies. The cumulative subject exposure from GE Healthcare sponsored clinical trials is presented in Table 2.

The number of subjects exposed are shown by medication dosing categories in Table 3. Most study subjects received a dose of 185 MBq ± 10%; approximately 154 subjects received a dose of 370 MBq ± 10%.

A summary of age and gender categories of the subject exposed in these clinical trials is presented in Table 4. Following completion of reproductive toxicity studies, demonstrating no

adverse effects on fertility or foetal development in rats or rabbits, females of childbearing potential were allowed into the Phase III studies if they utilized effective means of contraception.

A summary of exposure by ethnic origin is presented in Table 5.

The exposure numbers of special-population subjects enrolled in Vizamyl (Flutemetamol (^{18}F) Injection) clinical studies are summarized in Table 6. Pregnant and lactating women were excluded from the studies. Subjects who volunteered to undergo testing for the apolipoprotein E gene gave separate informed consent; a total of 380 subjects agreed. Nineteen subjects (2.5%) had a medical history indicating some form of renal impairment; of 725 subjects with available baseline serum creatinine results, 18 (2.5%) had an elevated value.

Table 2 Cumulative exposure

Treatment	**Patients**
Medicinal product	831
Comparator	0
Placebo	0
Total[a]	**831**

[a] Includes subjects from studies: ALZ103, ALZ201, GE067-005, GE067-007, GE067-008, GE067-009, GE067-010, GE067-011, GE067-014, GE067-015, GE067-017 and GE067-021.

Table 3 Exposure by dose

Dose of exposure, Injected Activity (MBq)	**Patients**
<90	0
≥90 to <110	8
≥110 to <135	21
≥135 to <166.5	21
≥166.5 to <203.5	594
≥203.5 to <333	33
≥333 to <407	154
≥407	0
Total[a]	**831**

[a] Includes subjects from studies: ALZ103, ALZ201, GE067-005, GE067-007, GE067-008, GE067-009, GE067-010, GE067-011, GE067-014, GE067-015, and GE067-017. MBq= megabecquerel

Table 4 Exposure by age group and gender

Age group	**Patients**	
Adults and elderly people	**Male**	**Female**
<40 years	80	103
≥40 years	321	327

Table 4 Exposure by age group and gender

Age group	**Patients**	
<65 years	159	182
≥65 years	242	248
<75 years	277	284
≥75 years	124	146
Total	401	430
Grand total[a]		**831**

[a] Includes subjects from studies: ALZ103, ALZ201, GE067-005, GE067-007, GE067-008, GE067-009, GE067-010, GE067-011, GE067-014, GE067-015, and GE067-017.

Table 5 Exposure by ethnic origin

Ethnic origin		**Patients[a]**
Race, n (%)	American Indian or Alaska Native	1 (<0.5)
	Asian	97 (12)
	Black	33 (4)
	Native Hawaiian or other Pacific Islander	1 (<0.5)
	White	693 (83)
	Other	6 (1)
Ethnicity, n (%)	Not Hispanic or Latino	557 (67)
	Hispanic or Latino	160 (19)
	Missing	114 (14)

[a] Includes subjects from studies: ALZ103, ALZ201, GE067-005, GE067-007, GE067-008, GE067-009, GE067-010, GE067-011, GE067-014, GE067-015, GE067-017 and GE067-021.

Table 6 Exposure in special populations

Special population group	**Patients**
Pregnant women	0
Lactating women	0
Renal impairment	19
Hepatic impairment	1
Cardiac impairment	9
Sub-populations with genetic polymorphism:	
Apolipoprotein e2/e2	1
Apolipoprotein e2/e3	28
Apolipoprotein e2/e4	6

Table 6 Exposure in special populations

Special population group	Patients
Apolipoprotein e3/e3	203
Apolipoprotein e3/e4	116
Apolipoprotein e4/e4	26
Total	**409**

Exposure in patients receiving more than one dose

The vast majority (98.5%) of subjects received only 1 dose of Vizamyl, 12 subjects (1.5%) received 2 doses, and no subject received more than 2 doses.

In study ALZ201, seven subjects each received 2 doses of Flutemetamol (^{18}F) Injection. The 7 subjects received a mean dose of 121 MBq for each of the 2 doses, giving a cumulative mean injected dose of 242 MBq. Following the second dose in the group of patients with probable AD, 14% (1 of 7) subjects experienced one adverse event (AE) (extravasation). The event led to a temporary discontinuation of study medication and was considered mild and unrelated to study medication.

In study GE067-017, a cohort of 5 subjects with probable AD received an initial administration of 120 MBq and a second administration of 120 MBq between 1 and 4 weeks after the first administration in order to test the inherent consistency of the uptake of Flutemetamol (^{18}F) Injection. One subject experienced upper respiratory tract inflammation after second administration. The event was considered mild and unrelated to study medication. Another subject experienced a serious event of lumbar pain after signing the informed consent form, more than two months before the study drug administration. A causal relationship with the study drug was ruled out. The same patient experienced moderate injection site extravasation one week after the first dose and a few minutes prior to the second injection. The event was considered unrelated to study medication.

In studies ALZ201 and GE067-017, no serious AEs (SAEs) or deaths occurred following the second dose of Flutemetamol (^{18}F) Injection. Due to the low number of AEs reported following the second dose, it would not be meaningful to compare the AE rate in the group who received 2 doses to the AE rate in the group of subjects who received only one dose.

Some therapeutic paradigms may necessitate multiple PET scans to support clinical decision-making, including the assessment of treatment continuation and dose optimization. In these situations, repeat administration of Vizamyl is anticipated to be limited to one or two additional doses. Based on current clinical expectations, repeat administrations would occur within an approximate 18-month period following the initial dose, with a minimum interval of six months between administrations. Given this limited frequency, the associated safety risks are considered minimal.

To date, no safety concerns have been identified in relation to repeated administration. However, the possibility that repeated PET imaging may become standard practice, particularly in the context of potential future therapeutic approvals requiring more frequent monitoring, warrants continued regulatory and clinical consideration.

Exposure in investigator-sponsored trials

A number of independent studies, where GE Healthcare is not the sponsor, are being conducted with Flutemetamol (^{18}F) Injection (in countries where the product is unlicensed) or Vizamyl (in countries where the product has marketing authorisation (MA)).

Cumulatively, it is estimated that 7939 subjects have received at least 1 dose Flutemetamol (^{18}F) injection / Vizamyl in investigator-sponsored clinical trials from the international birth date (IBD), 25 October 2013, up to 30 September 2025.

Module SIV - Populations not studied in clinical trials

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

The exclusion of the specified populations from the clinical studies of Flutemetamol (^{18}F) Injection is not considered to have any important consequences for the safety assessment of Vizamyl.

Patients 18 years of age or younger

Reason for exclusion:

Paediatric patients

Is it considered to be included as missing information?

No

Rationale:

Vizamyl is not intended for use in children. Intentional off-label use or unintended exposure is considered unlikely since brain amyloid, aMCI, and AD do not occur in paediatric patients.

Females who are pregnant or breast feeding

Reason for exclusion:

No pregnant or breast-feeding women were studied, as this is standard practice in clinical studies.

Is it considered to be included as missing information?

No

Rationale:

Vizamyl is intended for use in elderly persons, and therefore most women in the target population will be post-menopausal, and it is unlikely that any pregnant or lactating women will be exposed. In the unlikely event of pregnancy or breastfeeding in a patient being considered for amyloid imaging, it would be extremely unlikely that amyloid imaging could not be postponed until after birth or until after breast-feeding has finished.

Hypersensitivity to Flutemetamol (18F) Injection or any of its excipients

Reason for exclusion:

Patients with known hypersensitivity to Flutemetamol (^{18}F) Injection or any of its excipients should not receive Vizamyl.

Is it considered to be included as missing information?

No

Rationale:

Hypersensitivity was formerly considered an important identified risk of Vizamyl. It has later been reclassified as an identified risk not considered important as it is well-known with no need for additional pharmacovigilance or risk minimisation activities.

Significant neurological disease (other than MCI)

Patients with Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, brain tumour, supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities were excluded in 4 studies (46% of the total population: GE067-005, ALZ103, GE067-014, ALZ201)

Reason for exclusion:

Lack of relevance to the target population because amyloid was not a known factor in the pathophysiology of these medical conditions at the time when these studies were carried out.

Is it considered to be included as missing information?

No

Rationale:

Evidence from literature reports of amyloid imaging and clinical trials does not suggest a different safety profile in these populations.

Studies ALZ103 and GE067-014 were Phase 1 studies of the biodistribution and radiation dosimetry and explored the ability of Flutemetamol (^{18}F) Injection to discriminate between healthy volunteers and patients with clinical AD. To meet the study objectives with the small sample sizes, subjects without the main neurologic conditions of interest were excluded.

Study ALZ201 was a Phase 2 study that enrolled healthy volunteers and patients with aMCI or AD. Like in the Phase 1 studies, subjects not having the main diagnoses of interest were excluded. Study GE067-005 was a Phase 3 study of the time to convert from aMCI to AD. Accordingly, patients without aMCI were excluded.

Several studies have imaged amyloid in Parkinson's disease (PD) patients using [^{11}C]-labelled Pittsburgh Compound-B (PiB). [Campbell et al. 2013] found that patients with PD with cognitive impairment do not exhibit the same PiB binding pattern as participants with AD. [Johansson et al. 2008] reported that [^{11}C]PiB retention was not significantly increased in patients with early stage PD. [Gomperts et al. 2013] found that [^{11}C]PiB-determined amyloid burden does not distinguish between PD patient with or without non-dementia cognitive impairment. [Kotagal et al. 2012] used [^{11}C]PiB imaging to study a potential link between serotoninergic system degeneration in PD and development of cerebral amyloidopathy. [Petrou et al. 2012] concluded that in PD patients who are at risk for dementia, it is uncommon to see

amyloid levels as high as those seen in AD. [Burack et al. 2010] concluded from an autopsy study that [^{11}C]PiB's ability to specifically identify fibrillar amyloid in the setting of alpha-synucleinopathy (as occurs in PD) makes it valuable for studying the course of dementia in patients with Lewy body disorders. Seventeen subjects had neuropathological evidence of Lewy Body disease in Study GE067-007. No relationship between discordant interpretations and Lewy Body disease has been identified. Based on the above we conclude that the exclusion of patients with Parkinson's disease from a subset of the Flutemetamol (^{18}F) Injection clinical development program is not of concern.

Patients with normal pressure hydrocephalus were enrolled in Studies GE067-008, GE067-009, GE067-010 and GE067-011. Flutemetamol (^{18}F) was found to have good sensitivity and specificity in this population, so the exclusion of this population from other studies is not of concern.

[Stankoff et al. 2011] studied the binding of [^{11}C]PiB to myelin in multiple sclerosis (MS) and reported that loss of PiB binding paralleled myelin loss in MS lesions in the white matter, while no change in signal was reported in the grey matter. Because the grey matter signal is not expected to be impacted by MS, amyloid detection with flutemetamol (^{18}F) is not expected to be impacted, hence the exclusion of this population from other studies is not considered to be of concern.

We found no articles on the use of amyloid imaging in Huntington's disease, supranuclear palsy or seizure disorders.

Stroke or cerebrovascular disease

Patients with a previous history of clinically evident stroke or a relevant cerebrovascular disease by brain imaging were excluded in 3 studies (15% of the total population): ALZ103, GE067-014, ALZ201.

Reason for exclusion: Lack of relevance to the target population because amyloid is not a known factor in the pathophysiology of these medical conditions.

Is it considered to be included as missing information? No

Rationale: Evidence from literature reports of amyloid imaging does not suggest a different safety profile in these populations.

These lesions all involve the blood supply of the brain. Lesions may be ischemic (resulting in reduced blood delivery to one or more brain regions) or haemorrhagic (result in extravasation of blood from the vascular system). Theoretically, a haemorrhagic stroke could result in extravasation of an amyloid imaging agent, with consequent increased local activity. An ischemic stroke leaves brain tissue without blood. Acutely, this would reduce or eliminate distribution of an amyloid imaging agent to the affected brain region. However, an amyloid imaging agent would not be used in the setting of an acute stroke. The probability that a haemorrhagic stroke would occur during PET amyloid imaging is small. Moreover, if this did occur, the focus would be on treating the stroke rather than completing the amyloid examination.

The long-term effects of vascular lesions on amyloid imaging have been assessed. [Ly et al. 2012] reported more [^{11}C]PiB activity in the peri-infarct region than in the corresponding

contralateral region in patients with subacute ischemic strokes. Global [^{11}C]PiB uptake was not increased, however. Thus, interpretation of amyloid images would still be possible even in patients with ischemic strokes.

Based on the above we conclude that the exclusion of patients with cerebrovascular disease from the Flutemetamol (^{18}F) Injection clinical development program is not of concern.

Head injury with loss of consciousness

Patients with a history of head injury with loss of consciousness were excluded in 3 studies (15% of the total population): ALZ103, GE067-014, ALZ201.

Reason for exclusion:

Lack of relevance to the target population because amyloid is not a known factor in the pathophysiology of these medical conditions.

Is it considered to be included as missing information?

No

Rationale:

Evidence from literature reports of amyloid imaging does not suggest a different safety profile in these populations.

Traumatic brain injury (TBI) is believed to be a risk factor for the later development of AD, based on the finding that approximately 30% of patients who die from TBI have amyloid plaques [Sivanandam and Thakur. 2012]. [Kawai et al. 2013] obtained [^{11}C]PiB images on 12 patients with post-TBI neuropsychological impairment, and reported that images were positive in 25% (3 of 12) of the patients. They found no correlation between [^{11}C]PiB deposition and severity of injury. They suggested that serial amyloid PET examination may be useful in clarifying the temporal course of amyloid deposition in TBI.

Based on the above we conclude that the exclusion of patients with cerebrovascular disease from the Flutemetamol (^{18}F) Injection clinical development program is not of concern.

Brain abnormalities, infarcts or tumours

Patients with known or suspected structural brain abnormalities, such as infarcts or tumours, which may interfere with the interpretation of PET images were excluded in 1 study (24% of the total population): GE067-007.

Reason for exclusion: Initial concern that tumours might interfere with image interpretation. Tumours can, by mass effect, displace adjacent brain tissue, and thus may alter the appearance of flutemetamol (^{18}F) scans. Also, tumours are associated with disruption of the blood-brain barrier, which account for contrast enhancement seen on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) images.

Is it considered to be included as missing information? No

Rationale: Evidence from literature reports of amyloid imaging does not suggest a different safety profile in these populations.

It is unlikely that a patient with a tumour would undergo PET amyloid imaging without knowledge of the tumour's presence. First, masses often result in focal neurological defects, and a mass is likely to be suspected on clinical grounds. Second, amyloid imaging is intended for patients with cognitive impairment. Anatomic imaging (either MRI or CT) is part of the standard workup of patients with cognitive symptoms, to rule out masses and vascular pathology. Therefore, it is extremely unlikely that a physician who refers a patient to amyloid imaging would not be aware of an intracranial mass, or that this would not be communicated to the imaging physician who interprets the PET images.

We found two reports of amyloid imaging using [^{11}C]PiB in patients with intracranial masses (both meningiomas). [Yamamoto et al. 2013] reported finding a meningioma in a 69-year-old man with no history of neurologic or psychiatric disorders, who underwent [^{11}C]PiB PET imaging as a healthy volunteer for a clinical study. The PET images showed increased PiB signal in the left frontal region. MR images were consistent with meningioma. [Kim et al. 2012] reported focal increased PiB signal in the right anterior temporal region in an 83-year-old female healthy volunteer for a clinical study. MR images were consistent with a benign meningioma.

Based on the above we conclude that the exclusion of patients with tumours from the Flutemetamol (^{18}F) Injection clinical development program is justified.

Alcohol or drug abuse

Reason for exclusion:

Patients with known alcohol and drug abuse were not included in 4 studies (GE067-015, ALZ103, GE067-014, ALZ201, i.e., 39% of the total population), because this is standard practice in clinical studies.

Is it considered to be included as missing information?

No

Rationale:

The amount of alcohol in the product is very small and there is no abuse potential.

Significant psychiatric disorders

Reason for exclusion:

Patients with significant psychiatric disorders (including major depression, schizophrenia, mania, bipolar disorder, etc.), accounting for approximately 46% of the total population, were excluded in 4 studies (GE067-005, ALZ103, GE067-014, and ALZ201) as a significant psychiatric disease might have interfered with the study purpose. Study GE067-005 included subjects with aMCI and, ALZ103 included subjects with probable AD and healthy volunteers, and GE067-014 were phase 1 studies in AD subjects and healthy volunteers, while ALZ201 was a phase 2 study in subjects with probable AD, aMCI and healthy volunteers.

Is it considered to be included as missing information?

No

Rationale:

Significant psychiatric disease is not expected to impact on Vizamyl's ability to detect amyloid beta. Moreover, the use of Vizamyl in these populations is not expected, as the associated conditions are not considered to have a pathophysiological link to amyloid.

Positive for serum test of hepatitis B antigen, hepatitis C virus antibody, human immunodeficiency virus (HIV) antibody or Treponema pallidum Latex Agglutination

Reason for exclusion:

Patients that are positive for serum test of hepatitis B antigen, hepatitis C virus antibody, HIV antibody or Treponema pallidum Latex Agglutination were excluded in 2 studies (GE067-014, GE067-015; i.e., 27% of the total population) in order to ensure the safety of clinical trial and laboratory personnel handling patient blood samples.

Is it considered to be included as missing information?

No

Rationale:

These patients are not expected to constitute a significant part of the target population or to pose contraindications to the use of Vizamyl.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Table 7 discusses limitations of adverse drug reaction (ADR) detection in the Vizamyl/flutemetamol (^{18}F) clinical trial programme.

No relevant limitations of the clinical database have been identified. The size of the clinical trial database allows for detection of ADRs with a frequency greater than 1:277. Other potential limitations are not considered to be of relevance.

Table 7 Limitations of ADR detection

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
which are rare	Approx. 831 patients were exposed over the entire clinical trial program.	ADRs occurring with a frequency greater than 1 in 277 could be detected in a patient population of 831.
due to prolonged exposure	Not relevant.	N/A
due to cumulative effects	Not relevant.	N/A
which have long latency.	Lack of long-term follow-up.	N/A

These situations are considered not relevant because Vizamyl is intended for periodic infrequent single-dose administration for diagnostic purposes.

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

Table 8 presents exposure in the populations of patients that were excluded or under-represented when the safety of Vizamyl/flutemetamol (^{18}F) was studied in the clinical development programme.

Table 8 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	Not included in the clinical development programme.
Pregnant and breastfeeding women	Not included in the clinical development programme.
Patients with hepatic impairment	In the Vizamyl clinical development program, one subject had cirrhosis of the liver with ascites.
Patients with renal impairment	Nineteen subjects in the Vizamyl development program had renal impairment, and 18 subjects had elevated serum creatinine at baseline.
Patients with cardiovascular impairment:	In the Vizamyl clinical development program, nine subjects had cardiac impairment.
Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Not included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms:	Not included in the clinical development programme.
Other: Elderly	≥65 years – 490 patients <75 years – 561 patients ≥75 years – 270 patients

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The exposure data is estimated based on information from GE Healthcare Supply Chain Operations. Post-authorization exposure includes patients dosed with commercially marketed drug product worldwide, named patient use in several European Union (EU countries), and non-GE Healthcare sponsored clinical trials where Vizamyl was used as an auxiliary medicinal product. It is assumed that one kit is used for one single patient, except for the cassettes sold in Japan where the injectable solution from one cassette is used in approximately 2 patients.

SV.1.2 Exposure

The worldwide, cumulative estimation of post-authorisation patient exposure from the first marketing authorization on 25 October 2013 to data lock point 30 September 2025, is presented in Table 9. In total, it is estimated that more than 122000 patients have been exposed to Vizamyl post-marketing. Of these, approximately 105500 patients were dosed with Vizamyl from vials supplied by GE Healthcare or licensing partners, including 4363 patients that were provided with drug product on a named patient basis. In addition, in Japan, where the flutemetamol (^{18}F) synthesizing cassette is registered as a medical device, 731 cassettes have been supplied commercially. With approximately two doses administered per cassette, an estimated 1462 patients received doses manufactured by cassettes. Exposure from use of Vizamyl as an auxiliary/non-investigational medicinal product is presented separately, see below.

No data regarding dose, sex and age are available. It is reasonable to assume that adults aged beyond 40 years and elderly patients were exposed.

Table 9 Cumulative post-authorization patient exposure to Vizamyl from 25 October 2013 to 30 September 2025

Indication	**Formulation**		**Region**				**Total**
Cognitive impairment	Cassettes	IV	EU	Asia-Pacific	United States	Other	
Commercial use	1462	101135	31838	51439	18828	492	102597
Named patient use*	0	4363	4363	0	0	0	4363
Total	1462	105498	36201	51439	18828	492	106960

* Named patient use of the EU approved Vizamyl refers to use by individual health care professionals upon application in an EU member state where Vizamyl is not marketed.

Exposure in investigational clinical trials where Flutemetamol (18^F) injection is used as an auxiliary medicinal product

There are several ongoing investigational clinical trials where Vizamyl is being used as a biomarker (auxiliary/non-investigational medicinal product) in non-GE Healthcare sponsored studies, which were designed to evaluate investigational treatments for patients with cognitive impairment or possible early AD. Cumulatively, 15170 doses of Flutemetamol (^{18}F) Injection have been administered in such studies from the IBD (25 October 2013) up to 30 September 2025.

In the previous version of the RMP exposure information from these trials was included under Clinical trial exposure.

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

None. Vizamyl has no abuse potential. Chemically, flutemetamol (^{18}F) is a benzothiazole, a class of chemicals which is not known to hold abuse potential. Furthermore, distribution is highly controlled owing to its radioactive nature; the product is manufactured and dispensed

only in response to prescription and delivered directly to hospitals. Finally, the amount of flutemetamol (^{18}F) in a single dose is <1.5 µg and is too small to give any pharmacologic effects.

Module SVII - Identified and potential risks

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

The safety concerns included in the initial RMP for Vizamyl is listed in Table 10 below. In further updates of the Vizamyl RMP the safety profile has been revised and some risks have been removed from the list of safety concerns, see SVII.2 New safety concerns and reclassification with a submission of an updated RMP.

Table 10 List of safety concerns identified in the initial Vizamyl RMP

Important identified risk	Hypersensitivity
Important potential risk	PET imaging interpretation errors Carcinogenicity and hereditary defects Off-label usage
Missing information	Safety in patients with renal impairment Safety in patients with hepatic impairment Clinical experience in patients receiving more than one dose

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

The risks described in this section are not included in the list of safety concerns because they have minimal clinical impact on patients (in relation to the severity of the indication treated):

- PET imaging interpretation errors
- Embryo-foetal risk
- Potential harm from overdose
- Potential for medication errors
- Potential for transmission of infectious agents
- Potential for pharmacokinetic and pharmacodynamic interactions

PET imaging interpretation errors

Amyloid PET imaging with Vizamyl supports the diagnosis or exclusion of AD by detecting amyloid plaque deposition. However, like all diagnostic tools, it carries the risk of false-positive and false-negative results, which may lead to inappropriate clinical decisions. A false-positive scan may suggest amyloid pathology in individuals with other underlying causes with cognitive impairment. Conversely, a false-negative result may delay a diagnosis of AD and treatment. To mitigate these risks, Vizamyl's Summary of Product Characteristics (SmPC) includes detailed image interpretation guidelines and states that readers should be trained in the interpretation of PET images with Vizamyl. Readers are also advised to use anatomical imaging (Computed Tomography (CT) or MRI) to support interpretation.

Importantly, in the diagnostic workup of a patient, amyloid imaging results should always be considered in the context of the clinical presentation and other factors. AD is now understood as a biological continuum, integrating clinical symptoms with biomarker evidence. According to the 2024 revised criteria from the Alzheimer's Association and the National Institute on Aging, diagnosis requires validated biomarkers, such as amyloid and tau detected via CSF, PET, or plasma, in symptomatic individuals. These biomarkers support diagnosis but are not recommended for screening cognitively unimpaired individuals outside research settings [Hansson et al. 2022]. Clinical diagnosis alone has limitations, with misdiagnosis rates as high as 20–30%, underscoring the importance of biomarker confirmation for accurate assessment [Gaugler et al. 2013].

While Vizamyl can help rule out AD in the absence of amyloid, its clinical relevance has increased with the approval of disease-modifying therapies in both the United States and the European Union. Treatments such as lecanemab (Leqembi®) and donanemab (Kisunla™) are now authorized for early-stage AD in patients with confirmed amyloid pathology, offering the potential to slow cognitive decline. These therapies complement existing symptomatic treatments, such as cholinesterase inhibitors and memantine, which target neurotransmitter systems but do not alter disease progression. Overall, the benefit of early diagnostic support from amyloid imaging outweighs the low risk of misinterpretation, especially when used as part of a comprehensive diagnostic approach that includes biomarker confirmation.

False-positive and false-negative results with Vizamyl may impact clinical interpretation and subsequent patient management decisions. A false-positive result can lead to an incorrect diagnosis in patients with reversible causes of MCI or other underlying causes of cognitive decline, potentially causing psychological distress and unnecessary exposure to therapies. A false-negative result may delay diagnosis and treatment, missing the critical window for therapeutic intervention. These risks are particularly relevant now that therapies like lecanemab and donanemab are approved for early-stage AD in patients with confirmed amyloid pathology.

To address these concerns, Vizamyl's use is supported by rigorous reader training, detailed interpretation guidelines, and the integration of anatomical imaging. In addition, quantitation has been added as an adjunct to visual inspection and has the ability to increase reader confidence on the interpretation of the scan as well as assisting in scan assessment when the scan is equivocal [Bucci et al. 2021]. Amyloid PET imaging is not used in isolation but as part of a broader diagnostic framework that includes clinical evaluation and biomarker confirmation. Although no diagnostic tool is infallible, the structured use of Vizamyl within a multimodal approach enhances diagnostic accuracy and supports safer, more effective clinical decision-making.

"PET imaging interpretation errors" have been removed from the safety specification following a recommendation in the PSUR Assessment Report for Vizamyl (PSUSA/00010293/202410). PRAC and CHMP now consider misinterpretation of PET images to be an efficacy issue rather than a safety concern. Consequently, the educational material previously classified as an additional risk minimisation measure in the RMP and Annex II D will be removed. However, in line with PRAC's recommendation, the Marketing Authorisation Holder (MAH) will continue to offer training to healthcare professionals, as stated in section 4.4 of the Vizamyl

SmPC: “VIZAMYL images should only be interpreted by readers trained in the interpretation of PET images with flutemetamol (^{18}F).”

The benefit of facilitating early diagnosis of AD outweighs the potential risk of PET image interpretation errors, as imaging is one of several diagnostic tools and such errors occur infrequently. The Vizamyl image reader training program is expected to further reduce this risk.

Embryo-foetal risk

Although Vizamyl (flutemetamol (^{18}F)) is a radiopharmaceutical agent and radiation exposure during pregnancy is generally associated with potential risks to the embryo or foetus, this risk is not considered an important safety concern for inclusion in the RMP for the following reasons:

Vizamyl is indicated for diagnostic imaging in adult patients being evaluated for cognitive impairment, including AD. The patient population is predominantly older adults, including postmenopausal women, in whom pregnancy is highly unlikely. Therefore, the risk of inadvertent exposure during pregnancy is considered negligible.

The Vizamyl RSI includes clear guidance to assess pregnancy status prior to administration and advises against use during pregnancy unless the potential benefit outweighs the risk. These measures are considered adequate to mitigate the theoretical risk.

No reproductive or developmental toxicity studies have been conducted (see details in Table 1). Repeated dose toxicity studies in rats and dogs showed no adverse effects on reproductive organs, and radiation exposure to gonads was calculated to be very low (0.008 μSv/MBq), consistent with other diagnostic radiopharmaceuticals. Pregnant and breastfeeding subjects are excluded from clinical trials. No genotoxicity concerns have been identified.

The radiation dose associated with Vizamyl is low (approximately 5.92 mSv per scan), and the isotope has a short physical half-life (~110 minutes), which limits systemic exposure and potential risk to the foetus.

Neither the European Medicines Agency (EMA) nor the U.S. Food and Drug Administration (FDA) have identified embryo-foetal risk as an important safety concern in their respective assessments of Vizamyl. No additional pharmacovigilance activities or risk minimisation measures beyond routine labelling have been required.

Given the limited and controlled use of Vizamyl, the characteristics of the target population, and the absence of clinical or nonclinical safety signals, the potential for embryo-foetal harm is not considered an important identified or potential risk and is therefore excluded from the list of safety concerns in this RMP.

The potential for embryo-foetal harm with Vizamyl is considered minimal due to its low radiation dose, short half-life, and use in a population where pregnancy is rare. The diagnostic benefits in evaluating amyloid pathology in cognitively impaired adults outweigh this theoretical risk, especially with existing precautions such as pregnancy screening and labelling guidance.

Potential for harm from overdose, and misuse for illegal purposes

The recommended clinical dose is a single dose of approximately 185 MBq Vizamyl administered intravenously by qualified medical personnel in a hospital setting.
The total mass of administered material is in the microgram range, in contrast to therapeutic drugs where the mass is more typically in the milligram range. For Vizamyl, the mass of flutemetamol (^{18}F) in a typical dose is <1.5 μg (<5.5×10-9 moles) the total mass of flutemetamol (^{18}F) and related substances is <20 μg. No pharmacologic effects are intended, and none are observed. Because of the short radioactive half-life of Flutemetamol (^{18}F) Injection (approximately 110 minutes), Vizamyl must be manufactured, purified, and shipped within a single day. Doses will be prepared only on demand in response to a valid prescription for a patient. Radioactive drugs such as Vizamyl are strictly controlled and are shipped to and handled exclusively by the nuclear medicine department at a healthcare institution. In the clinical studies, the range of administered activity was 93.4 to 403.3 MBq, with a median of 183.50 MBq.

Potential for medication errors

The potential for medication errors is minimal due to single administration for diagnostic purposes by a healthcare professional. Like all diagnostic radiopharmaceuticals, Vizamyl is only available by prescription. It is manufactured only as needed, owing to the short radioactive half-life. Vizamyl is shipped only to facilities with appropriate licences for handling radioactive materials and which have personnel with the appropriate training, experience, and licensing to handle radioactive materials including diagnostic radiopharmaceuticals. Radioactive materials are kept in controlled environments in the nuclear medicine department of the hospital or clinic where they are used. Trained technologists or physicians prepare and administer the doses of radiopharmaceuticals. The avoidance of medication errors relies on the training and diligence of healthcare personnel.

Potential for transmission of infectious agents

Vizamyl is a ready-to-use sterile formulation and any possible contamination with infectious agents is effectively eliminated and controlled during the manufacturing process. It is produced by chemical synthesis and its preparation does not involve biologics or chemicals derived from living organisms. In clinical use, the risk of transmission of infectious agents will be mainly related to the technique used by the medical personnel preparing and injecting the product.

Potential for pharmacokinetic and pharmacodynamic interactions

The target populations for Vizamyl are likely to be on multiple medications due to common co-morbidities like vascular disease, cancer, and disturbed thyroid function. However, drug interactions are considered extremely unlikely given the tracer levels of the active ingredient, Flutemetamol (^{18}F) Injection (<1.5 μg; <5.5×10-9 moles), and the rapid clearance of flutemetamol (^{18}F) is from the circulation after intravenous injection. The elimination half-life from plasma is 4.5 hours whereas the radioactive half-life of flutemetamol (^{18}F) is approximately 110 minutes.

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

There are no important identified or potential risks or missing information included in the list of safety concerns for Vizamyl.

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

“PET imaging interpretation errors” previously classified as an important potential risk is removed from the list of safety concerns.

The reason for the removal of this risk is a regulatory request from PRAC following PSUSA00010293202410 (EU PSUR dlp 31Ot 2024) as it is considered as an efficacy issue and not a safety issue. Further, PRAC requested that the educational material should be removed as an additional risk minimisation measure from the RMP.

For changes in safety concerns over time, please see Annex 8.

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

There are no important identified risks, important potential risks, or missing information included in the safety specification in this RMP.

Module SVIII - Summary of the safety concerns

Table 11 presents a summary of the safety concerns identified for Vizamyl.

Table 11 Summary of safety concerns (updated since the initial RMP)

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

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed, planned or ongoing.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned or ongoing.

III.3 Summary Table of additional Pharmacovigilance activities

No additional pharmacovigilance activities are planned or ongoing.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are planned or ongoing.

PART V:RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Not applicable for Vizamyl as there are no important risks identified in the summary of safety concerns in the RMP.

V.2 Additional risk minimisation measures

None.

V.3 Summary table of risk minimisation measures

Not applicable for Vizamyl as there are no important risks identified in the summary of safety concerns in the RMP.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VIZAMYL (FLUTEMETAMOL (^{18}F))

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

Vizamyl's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Vizamyl should be used.

This summary of the RMP for Vizamyl 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 Vizamyl's RMP.

I. The medicine and what it is used for

Vizamyl 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 (see SmPC for the full indication). It contains flutemetamol (^{18}F) as the active substance and it is given by intravenous route of administration.

Further information about the evaluation of Vizamyl's benefits can be found in Vizamyl's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/Vizamyl.

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

Important risks of Vizamyl, together with measures to minimise such risks and the proposed studies for learning more about Vizamyl'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 authorized 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 minimize 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

For Vizamyl, there are currently no important risks identified in the RMP. All other risks and missing information identified for Vizamyl are known risks that require no further characterisation, and no additional pharmacovigilance activities or additional risk minimisation measures, beyond routine pharmacovigilance.

Important risks of Vizamyl 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 Vizamyl. 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 as there are no important risks for Vizamyl.

II.C Post-authorisation development plan

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

There are no studies that are conditions of the marketing authorisation or specific obligation of Vizamyl.

II.C.1 Other studies in post-authorisation development plan

There are no studies required for Vizamyl.

PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable. No additional risk minimisation activities have been proposed.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

List of references

Full text articles to be provided upon request.

[Alzheimer's Association. 2025]

Alzheimer's Association. About Alzheimer's and Dementia: Medications for Memory, Cognition and Dementia-Related Behaviors 2025 [Available from: https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory.

[Alzheimer Europe. 2019]

Alzheimer Europe. Dementia in Europe Yearbook 2019, Estimating the prevalence of dementia in Europe 2019 [Available from: https://www.alzheimer-europe.org/sites/default/files/alzheimer_europe_dementia_in_europe_yearbook_2019.pdf.

[Alzheimer's Association. 2025]

Alzheimer's Association. 2025 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2025;21(5). 2025 [Available from: https://www.alz.org/getmedia/ef8f48f9-ad36-48ea-87f9-b74034635c1e/alzheimers-facts-and-figures.pdf.

[Alzheimer's Association. 2018]

Alzheimer's Association. Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia: Journal of the Alzheimer's Association. 2018;14:367–429.

[Being Patient. 2025]

Being Patient. Alzheimer's Treatments 2025: Here's Every FDA-Approved Therapy and What Comes Next 2025 [Available from: https://beingpatient.com/alzheimers-treatments-2025-your-guide-to-every-fda-approved-therapy/.

[Bucci et al. 2021]

Bucci M, Savitcheva I, Farrar G, Salvadó G, Collij L, Doré V, Gispert JD, Gunn R, Hanseeuw B, Hansson O, Shekari M, Lhommel R, Molinuevo JL, Rowe C, Sur C, Whittington A, Buckley C, Nordberg A. A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [(18)F]flutemetamol amyloid PET images. Eur J Nucl Med Mol Imaging. 2021;48(7):2183–99.

[Burack et al. 2010]

Burack MA, Hartlein J, Flores HP, Taylor-Reinwald L, Perlmutter JS, Cairns NJ. In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology. 2010;74(1):77–84.

[Campbell et al. 2013]

Campbell MC, Markham J, Flores H, Hartlein JM, Goate AM, Cairns NJ, Videen TO, Perlmutter JS. Principal component analysis of PiB distribution in Parkinson and Alzheimer diseases. Neurology. 2013;81(6):520–7.

[Dickerson and Wolk. 2013]

Dickerson BC, Wolk DA. Biomarker-based prediction of progression in MCI: Comparison of AD signature and hippocampal volume with spinal fluid amyloid-β and tau. Front Aging Neurosci. 2013;5:55.

[Dubois et al. 2024]

Dubois B, Villain N, Schneider L, Fox N, Campbell N, Galasko D, Kivipelto M, Jessen F, Hanseeuw B, Boada M, Barkhof F, Nordberg A, Froelich L, Waldemar G, Frederiksen KS, Padovani A, Planche V, Rowe C, Bejanin A, Ibanez A, Cappa S, Caramelli P, Nitrini R, Allegri R, Slachevsky A, de Souza LC, Bozoki A, Widera E, Blennow K, Ritchie C, Agronin M, Lopera F, Delano-Wood L, Bombois S, Levy R, Thambisetty M, Georges J, Jones DT, Lavretsky H, Schott J, Gatchel J, Swantek S, Newhouse P, Feldman HH, Frisoni GB. Alzheimer Disease as a Clinical-Biological Construct-An International Working Group Recommendation. JAMA Neurol. 2024;81(12):1304–11.

[Gaugler et al. 2013]

Gaugler JE, Ascher-Svanum H, Roth DL, Fafowora T, Siderowf A, Beach TG. Characteristics of patients misdiagnosed with Alzheimer's disease and their medication use: an analysis of the NACC-UDS database. BMC Geriatr. 2013;13:137.

[Global Burden of Disease Study. 2022]

Global Burden of Disease Study. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022;7(2):e105–e25.

[Gomperts et al. 2013]

Gomperts SN, Locascio JJ, Rentz D, Santarlasci A, Marquie M, Johnson KA, Growdon JH. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. Neurology. 2013;80(1):85–91.

[Hanseeuw et al. 2019]

Hanseeuw BJ, Betensky RA, Jacobs HIL, Schultz AP, Sepulcre J, Becker JA, Cosio DMO, Farrell M, Quiroz YT, Mormino EC, Buckley RF, Papp KV, Amariglio RA, Dewachter I, Ivanoiu A, Huijbers W, Hedden T, Marshall GA, Chhatwal JP, Rentz DM, Sperling RA, Johnson K. Association of Amyloid and Tau With Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. JAMA Neurol. 2019;76(8):915–24.

[Hansson et al. 2022]

Hansson O, Edelmayer RM, Boxer AL, Carrillo MC, Mielke MM, Rabinovici GD, Salloway S, Sperling R, Zetterberg H, Teunissen CE. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimers Dement. 2022;18(12):2669–86.

[Huszár et al. 2024]

Huszár Z, Engh MA, Pavlekovics M, Sato T, Steenkamp Y, Hanseeuw B, Terebessy T, Molnár Z, Hegyi P, Csukly G. Risk of conversion to mild cognitive impairment or dementia among subjects with amyloid and tau pathology: a systematic review and meta-analysis. Alzheimers Res Ther. 2024;16(1):81.

[Jack et al. 2024]

Jack CR, Jr., Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, Hansson O, Ho C, Jagust W, McDade E, Molinuevo JL, Okonkwo OC, Pani L, Rafii MS, Scheltens P, Siemers E, Snyder HM, Sperling R, Teunissen CE, Carrillo MC. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024;20(8):5143–69.

[Johansson et al. 2008]

Johansson A, Savitcheva I, Forsberg A, Engler H, Langstrom B, Nordberg A, Askmark H. [(11)C]-PIB imaging in patients with Parkinson's disease: preliminary results. Parkinsonism Relat Disord. 2008;14(4):345–7.

[Kawai et al. 2013]

Kawai N, Kawanishi M, Kudomi N, Maeda Y, Yamamoto Y, Nishiyama Y, Tamiya T. Detection of brain amyloid beta deposition in patients with neuropsychological impairment after traumatic brain injury: PET evaluation using Pittsburgh Compound-B. Brain Inj. 2013;27(9):1026–31.

[Kim et al. 2012]

Kim HY, Kim J, Lee JH. Incidental finding of meningioma on C11-PIB PET. Clin Nucl Med. 2012;37(2):e36–7.

[Kotagal et al. 2012]

Kotagal V, Bohnen NI, Muller ML, Koeppe RA, Frey KA, Albin RL. Cerebral amyloid deposition and serotoninergic innervation in Parkinson disease. Arch Neurol. 2012;69(12):1628–31.

[Liu et al. 2025]

Liu W, Deng W, Gong X, Ou J, Yu S, Chen S. Global burden of Alzheimer's disease and other dementias in adults aged 65 years and over, and health inequality related to SDI, 1990-2021: analysis of data from GBD 2021. BMC Public Health. 2025;25(1):1256.

[Livingston et al. 2024]

Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C, Fox NC, Ferri CP, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Nakasujja N, Rockwood K, Samus Q, Shirai K, Singh-Manoux A, Schneider LS, Walsh S, Yao Y, Sommerlad A, Mukadam N. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet. 2024;404(10452):572–628.

[Ly et al. 2012]

Ly JV, Rowe CC, Villemagne VL, Zavala JA, Ma H, Sahathevan R, O'Keefe G, Gong SJ, Gunawan R, Churilov L, Saunder T, Ackerman U, Tochon-Danguy H, Donnan GA. Subacute ischemic stroke is associated with focal 11C PiB positron emission tomography retention but not with global neocortical Abeta deposition. Stroke. 2012;43(5):1341–6.

[National Institute on Aging. 2023]

National Institute on Aging. How Is Alzheimer's Disease Treated? 2023 [Available from: https://www.nia.nih.gov/health/alzheimers-treatment/how-alzheimers-disease-treated.

[Petrou et al. 2012]

Petrou M, Bohnen NI, Muller ML, Koeppe RA, Albin RL, Frey KA. Abeta-amyloid deposition in patients with Parkinson disease at risk for development of dementia. Neurology. 2012;79(11):1161–7.

[Sivanandam and Thakur. 2012]

Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer's disease. Neurosci Biobehav Rev. 2012;36(5):1376–81.

[Stankoff et al. 2011]

Stankoff B, Freeman L, Aigrot MS, Chardain A, Dolle F, Williams A, Galanaud D, Armand L, Lehericy S, Lubetzki C, Zalc B, Bottlaender M. Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-(1)(1)C]-2-(4'-methylaminophenyl)- 6-hydroxybenzothiazole. Ann Neurol. 2011;69(4):673–80.

[U.S. FDA. 2023]

U.S. FDA. FDA Approves First Drug to Treat Agitation Symptoms Associated with Dementia due to Alzheimer's Disease 2023 [Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-agitation-symptoms-associated-dementia-due-alzheimers-disease.

[U.S. FDA. 2024]

U.S. FDA. FDA approves treatment for adults with Alzheimer's disease 2024 [Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease.

[van Maurik et al. 2019]

van Maurik IS, van der Kall LM, de Wilde A, Bouwman FH, Scheltens P, van Berckel BNM, Berkhof J, van der Flier WM. Added value of amyloid PET in individualized risk predictions for MCI patients. Alzheimers Dement (Amst). 2019;11:529–37.

[WHO Regional Office for Europe. 2025]

WHO Regional Office for Europe. European health report 2024: keeping health high on the agenda. Copenhagen2025 [Available from: file:///C:/Users/212738905/Downloads/9789289061704-eng.pdf.

[Winblad et al. 2016]

Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jonsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016;15(5):455–532.

[Wolk et al. 2018]

Wolk DA, Sadowsky C, Safirstein B, Rinne JO, Duara R, Perry R, Agronin M, Gamez J, Shi J, Ivanoiu A, Minthon L, Walker Z, Hasselbalch S, Holmes C, Sabbagh M, Albert M, Fleisher A, Loughlin P, Triau E, Frey K, Høgh P, Bozoki A, Bullock R, Salmon E, Farrar G, Buckley CJ, Zanette M, Sherwin PF, Cherubini A, Inglis F. Use of Flutemetamol F 18-Labeled Positron Emission Tomography and Other Biomarkers to Assess Risk of Clinical Progression in Patients With Amnestic Mild Cognitive Impairment. JAMA Neurol. 2018;75(9):1114–23.

[Wolters et al. 2020]

Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, Bis JC, Blacker D, Bos D, Brayne C, Dartigues JF, Darweesh SKL, Davis-Plourde KL, de Wolf F, Debette S, Dufouil C, Fornage M, Goudsmit J, Grasset L, Gudnason V, Hadjichrysanthou C, Helmer C, Ikram MA, Ikram MK, Joas E, Kern S, Kuller LH, Launer L, Lopez OL, Matthews FE, McRae-McKee K, Meirelles O, Mosley TH, Jr., Pase MP, Psaty BM, Satizabal CL, Seshadri S, Skoog I, Stephan BCM, Wetterberg H, Wong MM, Zettergren A, Hofman A. Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium. Neurology. 2020;95(5):e519–e31.

[World Health Organization. 2022]

World Health Organization. A blueprint for dementia research 2022 [Available from: https://iris.who.int/server/api/core/bitstreams/8d77bf72-3b8b-4fbd-af48-d4734ccf53c1/content.

[World Health Organization. 2024]

World Health Organization. Fact sheets: The top 10 causes of death 2024 [Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

[Yamamoto et al. 2013]

Yamamoto Y, Maeda Y, Kawai N, Kudomi N, Nishiyama Y. Unexpected finding of cerebral meningioma on (11)C-PiB PET. Clin Nucl Med. 2013;38(4):292–3.