DaTSCAN 74 MBq/ml solution for injection

GE Healthcare

Generic name: ioflupane (^{123}I)

CORE RISK MANAGEMENT PLAN (RMP)

Date of report: **12 November 2020**

RMP Version number: **Version 1.0**

Data lock point for this RMP: **31 December 2019**

Marketing Authorisation Holder:

GE Healthcare B.V.

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(^{123}I)	Radioactive isotope iodine-123
^{123}I-FP-CIT	^{123}I-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane, ioflupane (^{123}I), DaTSCAN
AD	Alzheimer's disease
ADR	Adverse Drug Reaction
CCSI	Company Core Safety Information
CI	Confidence Interval
CT	Computed Tomography
COMT	Catechol-O-Methyltransferase
DAT	Dopamine transporter
DLB	Dementia with Lewy bodies
DNA	Deoxyribonucleic Acid
EAGM	Eastern and African Growth Markets
EEA	European Economic Area
ET	Essential Tremor
EU	European Union
FDG	Fludeoxyglucose
GAED	Global Adverse Event Database
GE	General Electric
GEHC	General Electric Healthcare
GLP	Good Laboratory Practice
hERG	human *Ether-à-go-go*-Related Gene
I*CH*	International Conference on Harmonisation
INN	International Non-proprietary Name
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MAO-B	Monoamine Oxidase B
MBq	Megabecquerel
mCi	MilliCurie
mGy	milliGray
*m*IBG	*meta*-iodobenzylguanidine
MRI	Magnetic Resonance Imaging
NOAEL	No-observed-adverse-effect-level
PET	Positron Emission Tomography
PD	Parkinson's Disease
PSP	Progressive Supranuclear Palsy
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPECT	Single-photon emission computed tomography
QPPV	Qualified Person for Pharmacovigilance

EU RISK MANAGEMENT PLAN FOR DATSCAN ioflupane (^{123}I)

RMP version to be assessed as part of this application:

RMP Version number:	1.0
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Version number:	N/A
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Date of approval (opinion date):	N/A

QPPV Name:	Burkhard Roessink (MD)

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

PART I: PRODUCT OVERVIEW

Table 1 Product overview

Active substance(s) (INN or common name)	ioflupane (123I)
Pharmacotherapeutic group(s) (ATC Code)	Diagnostic radiopharmaceutical central nervous system ATC code: V09AB03
Marketing Authorisation Holder	GE Healthcare B.V. De Rondom 8 5612 AP, Eindhoven The Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	DaTSCAN 74 MBq/ml solution for injection
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Radiopharmaceutical
	Summary of mode of action The active component in DaTSCAN, ioflupane (^{123}I) is a radio-iodinated cocaine analogue. ioflupane (^{123}I) distributes to the brain and preferentially binds to the presynaptic dopamine transporter (DAT) located predominantly on the nigrostriatal dopaminergic neurons. In healthy humans, this results in visualisation of the striata as two "comma"- or "half-moon"-shaped areas of brightness on SPECT imaging. However, loss of the nigrostriatal dopaminergic neurons (e.g. in Parkinson's disease or dementia with Lewy bodies) results in loss of the DAT associated with those neurons. This results in the absence of signal where it normally would be expected.
	Important information about its composition Ioflupane (^{123}I), 185 or 370 MBq at reference time. Iodine-123 has a physical half-life of 13.2 hours. It decays emitting gamma radiation with a predominant energy of 159 keV and X-rays of 27 keV.
Hyperlink to the Product Information	The proposed SmPC is included in the eCTD sequence with the name "ema-combined-h266-en-annotated"

Table 1 Product overview

Indication(s) in the EEA	**Current:** This medicinal product is for diagnostic use only. DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum: • In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. • In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. DaTSCAN is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.
	Proposed: Same as current
Dosage in the EEA	<u>Posology</u> Clinical efficacy has been demonstrated across the range 111 to 185 MBq. Should not exceed 185 MBq or be used when the activity is below 110 MBq. <u>Method of Administration</u> For intravenous use. DaTSCAN should be used without dilution. To minimise the potential for pain at the injection site during administration, a slow intravenous injection (not less than 15 to 20 seconds) via an arm vein is recommended.
	Proposed: N/A
Pharmaceutical form(s) and strengths	**Current:** Solution for injection Clear colourless solution Each 2.5 ml single dose vial contains 185 MBq ioflupane (^{123}I) (specific activity range 2.5 to 4.5 x 10^{14} Bq/mmol) at reference time. Each 5 ml single dose vial contains 370 MBq ioflupane (^{123}I) (specific activity range 2.5 to 4.5 x 10^{14} Bq/mmol) at reference time.
	Proposed: N/A
Will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the indications and target populations

Parkinson's Disease, Parkinsonian Syndromes, and Essential Tremor

Parkinson's disease (PD) is characterised by loss of dopaminergic neurons in substantia nigra pars compacta. The disease is characterised by presence of Lewy bodies and neurites which are composed of the protein alpha synuclein.

The diagnosis of PD is mostly based on history and clinical examination. The most common symptoms are Slowness, Tremor, Soft voice, Gait changes and Decreased fascial expression. On examination, findings are Bradykinesia, Rigidity and/or Tremor. However, the symptoms are not clear in all patients especially in early part of the disease. Both clinical and pathological studies have shown that PD is over diagnosed in up to 25% of cases [Marsili et al. 2018], [Rizzo et al 2016].

There are many therapeutic options for treating PD. This includes dopamine replacement with Carbidopa-levodopa, Dopamine agonist, catechol-O-methyltransferase (COMT) inhibitor and monoamine oxidase B (MAO-B) inhibitors.

Incidence

An estimated 4 percent of people with PD are diagnosed before age 50. Every year, about 60,000 Americans are diagnosed with PD, with about 6,600 new cases of PD diagnosed each year in Canada (based on an annual incidence of 20 new cases per 100,000 people) [Parkinson's News Today - Parkinson's Disease Statistics]. Crude annual incidence estimates for 39 European countries ranged from 5 per 100,000 to 346 per 100,000 [von Campenhausen et al. 2005].

Prevalence

Essential tremor (ET) is reportedly the most common movement disorder, with an estimated prevalence greater than 5% in individuals older than 65 years of age [Algarni et al. 2017]. A meta-analysis of 28 population-based prevalence studies revealed an overall prevalence of essential tremor of 0.9% (95% CI 0.5% to 1.5%) across all ages [Louis and Ferreira. 2010]. In those aged 60 years and older, the prevalence has been estimated to range from 1.3% to 5% [Louis et al. 1998].

PD is the second most common neurodegenerative disorder [de Lau and Breteler. 2006]. The prevalence of PD is about 0.3% of the whole population in industrialised countries.

In Western Europe's five most populous nations (Germany, France, the United Kingdom, Italy and Spain) and the world's 10 most populous nations (e.g. China, India, United States, Indonesia, Brazil, Russia, Japan), a conservative estimate of the number of individuals with PD over age 50 was between 4.1 and 4.6 million in 2005 [Dorsey et al. 2007]. In a recent systemic analysis on global burden of disease study found an estimated 6.1 million individuals globally with PD diagnosis in 2016, 2.4 times higher than in 1990. Age-standardised prevalence rates increased by 21.7% over the same period, indicating that the rise was not solely due to increased numbers of older people. The increasing prevalence was attributed to improved methods used to detect and diagnose PD, greater awareness of the disease, aging populations, longer life expectancy, and possibly increased environmental exposures (e.g. pesticides, solvents, metals) associated with industrialization [GBD. 2016]. It is estimated that approximately 930,000 people will be living with a PD diagnosis in the United States in 2020 [Armstrong and Okun. 2020]. Crude prevalence rate estimates for Europe ranged from 65.6 per 100,000 to 12,500 per 100,000 [von Campenhausen et al. 2005].

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The incidence of PD is linked to risk and protective factors. The most important risk factor is age, but the risk of PD also appears to be associated with industrial chemicals and pollutants, such as pesticides, solvents, and metals. Conversely, smoking is associated with a decreased risk of PD, but whether this association is causal is debatable [GBD. 2016].

PD is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80 [de Lau and Breteler. 2006]. PD is less common among individuals below the age of 50 and its prevalence increases with age. This is also more common in men (1.4 to 1 male to female ratio) [GBD. 2016]

The main existing imaging options

No neuroimaging technique is specifically recommended for routine use in clinical practice for PD [Pagano et al. 2016].

- ^{123}I-FP-CIT (DaTSCAN ^{TM}) single-photon emission computed tomography (SPECT) can be used in the differential diagnosis between PD and non-degenerative forms of parkinsonism. DaTSCAN SPECT should be considered in differential diagnosis between degenerative and nondegenerative parkinsonism in patients with tremor
- Brain magnetic resonance imaging (MRI), cardiac ^{123}I-mIBG SPECT and ^{18}F-FDG positron emission tomography (PET) have the potential to differentiate PD from atypical parkinsonism.
    - Brain MRI is helpful to detect cerebrovascular damages and to quantify brain atrophy in patients with parkinsonism. MRI is needed to identify the presence of a structural lesion (or lesions) that may cause or contribute to parkinsonism, gait disorder and tremor and should be considered in differential diagnosis between PD and other types of parkinsonism.

- Cardiac ^{123}I-*m*IBG SPECT and ^{18} F-FDG PET scanning should be considered in differential diagnosis between PD and atypical forms of degenerative parkinsonism (multiple system atrophy striatonigral degeneration, progressive supranuclear palsy).

- PET imaging provides the means to discriminate and reveal sub-phenotypes of PD and associations with non-dopaminergic deficits.

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

Progression of PD varies. Increasing evidence suggests that PD has heterogenous subtypes. Most of the patients have mild motor predominant (49%-53%), followed by the intermediate form (35%-39%) and the diffuse malignant form is least common (9%-16%). Patients with mild motor predominant form of the disease normally has good response to the treatment and are expected to have normal life expectancy. The patients in other two groups could progress quickly have lesser response to medications. However, patients in clinical practice are not categorised in this manner. But this description represents variability of the disease and could help counselling the patients regarding variability of symptoms, medication responsiveness and progression [Armstrong and Okun. 2020].

The aetiology of essential tremor (ET) is unknown, but evidence exists implicating ageing, genetics, and environmental toxins. A positive family history has been found in 17% to 100% of patients [Findley. 2000]. The pathophysiology of essential tremor (ET) has not been defined, but various lines of evidence implicate the involvement of the cerebellum, brainstem, and thalamus [Louis. 2001]. The age onset of ET is biomodal. Early-onset ET cases more commonly have a family history of tremor, whereas late-onset ET cases seem to have a faster rate of tremor progression and a higher risk for dementia [Louis et al. 2000], [Bermejo-Pareja et al. 2007], [Deuschl et al. 2015],[Louis et al. 2007].

Movement disorder society consensus statement describes the following diagnostic criteria for ET [Bhatia et al. 2018]:

1. Isolated tremor syndrome of bilateral upper limb action tremor
2. At least 3 years' duration
3. With or without tremor in other locations (e.g., head, voice, or lower limbs)
4. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.

ET and PD are each common disorders especially in the aging population and although they are thought to be mutually exclusive, they can have overlapping features which can make it difficult to differentiate between the two [Algarni et al. 2017].

Important co-morbidities

A retrospective study conducted by [Lubomski et al. 2015] for patients with idiopathic PD and a control group of non-PD patients admitted for acute care to New South Wales hospitals

between 2008 and 2012 found that patients with PD were five times more likely to be treated for delirium, three times more likely to experience an adverse drug event and syncope, more than twice as likely to require management of falls/fractures, dementia, gastrointestinal complications, genitourinary infections, reduced mobility and other trauma but half as likely to require hospitalization for chronic airways disease and neoplasia, including melanoma, than the control group (all $p<0.001$).

Dementia with Lewy Bodies

Incidence

There are very few studies on the incidence of dementia with Lewy bodies (DLB). Miech and colleagues [Miech et al. 2002] found that the incidence of DLB was 0.1% per year for the general population and 3.2% per year for all new cases of dementia.

Prevalence

Estimates of the prevalence of DLB are complicated by the lack of clearly defined clinical criteria and there are no clear numbers concerning the prevalence of Lewy body dementia. Substantial variation in the prevalence of DLB (depending on case criteria) has been reported with estimates ranging from 15% to 30% of all dementia cases worldwide, potentially making it the second most common dementia subtype [Aarsland et al. 2008]. According to the reports on the frequency of occurrence of DLB in non-population-based studies, estimates for prevalence varied between 3.0% and 26.3% [Zaccai et al. 2005] of all demented cases over the age of 65 years. This is similar to estimates from autopsy series, which have ranged between 15 and 25% [Zaccai et al. 2005].

Prevalence rates reported in studies by neurologists (0%–2.8%) are usually different from those reported by other specialists, such as psychiatrists and geriatricians (3.6%–30.5%) [Zaccai et al. 2005]. It may be due to a different emphasis on clinical phenotypes while diagnosing DLB: psychiatrists pay more attention to psychiatric symptoms and neurologists to neurological ones.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

A few factors seem to increase the risk of developing Lewy body dementia, including:

- Age - People older than 60 are at greater risk.
- Sex - Lewy body dementia affects more men than women.
- Family history - Those who have a family member with Lewy body dementia or PD are at greater risk.

The main existing imaging options

No neuroimaging technique is specifically recommended for routine use in clinical practice for Lewy Body Dementia [LBDA - Brain Imaging for Lewy Body Dementia].

- Computed tomography (CT) scans and MRIs are helpful tools physicians use to examine structural brain changes. MRIs provide superior images compared with CT scans in detecting structural problems in the brain. Most degenerative causes of dementia such as Alzheimer's disease and DLB are characterized by atrophy or shrinkage of the brain due to cell death. However, the patterns are similar so that the MRI cannot distinguish between Alzheimer's and DLB but can provide supporting evidence that the patient's symptoms are not due to another structural lesion. This is important because some causes of dementia such as hydrocephalus and brain tumors are potentially reversible if caught and treated early. In the early stages of DLB the atrophy can be very subtle. In the more advanced stages of dementia, the atrophy can be quite severe.
- ^{123}I-FP-CIT (DaTSCAN) is used to differentiate DLB from Alzheimer's. The DAT scan detects changes in the dopamine transporter in striatum responsible for allowing brain cells take up dopamine. DaTSCAN in abnormal in LBD. In the recently revised 4TH consensus criteria for diagnosis of DLB, DaT SPECT imaging is the recommended biomarker along with MIBG and polysomnic confirmation of REM sleep without atonia [McKeith et al. 2017].
- ^{18}F-FDG PET attaches radioactive fluorine to a specialized sugar that can be taken up by brain cells but not metabolized, therefore it gets "stuck" in the cells and can be imaged with the PET camera. In Alzheimer's, there is less metabolism in the posterior part of the brain called the parietal lobe. Furthermore, many DLB patients who hallucinate may have decreased brain metabolism in the visual part of the brain called the occipital lobe.

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

Rate of progression of Lewy body dementia varies significantly per person [McKeith et al. 2017].

Early Stages - In general, the earlier stages of Lewy body dementia may involve hallucinations or other distortions of reality such as delusions, restlessness, acting out dreams during sleep (called rapid eye movements sleep disorder), and some movement difficulties. Some people may appear to "freeze" or get stuck as they're moving around, and others may develop urinary urgency and incontinence. Unlike Alzheimer's disease, memory is usually still pretty intact in the early stages, although confusion and some mild cognitive changes may be present.

Middle Stages - As Lewy body dementia progresses towards its middle stages, some patients develop symptoms of tremors like PD, postural instability and falls, difficulty with speech, impaired ability to swallow and increased paranoia and delusions. Cognition also continues to decline, and these changes often include decreased attention and significant periods of confusion.

Later Stages - In the later symptoms of Lewy body dementia, extreme muscle rigidity and sensitivity to touch develops. Care becomes necessary for almost all activities of daily living. Speech is often very difficult and maybe whispered or absent. Lewy body dementia typically causes the individual to become very susceptible to pneumonia and other infections due to weakness, which may eventually be the cause of death [Manabe et al. 2016].

Important co-morbidities

[Fereshtehnejad et al. 2014] indicated a worse comorbidity profile in DLB patients with higher occurrence of depression, stroke and migraine compared with the AD group. "Mental and behavioural disorders", "diseases of the nervous system", "diseases of the eye and adnexa", diseases of the "circulatory", "respiratory", and "genitourinary" systems, "diseases of the skin and subcutaneous tissue" and "diseases of the musculoskeletal system and connective tissue" occurred more frequently in the DLB group after multivariate adjustment.

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

In routine diagnostic use, DaTSCAN is administered by slow intravenous injection (not less than 15 to 20 seconds) in a dose of 111 to 185 MBq (3 to 5 mCi). It is not intended for use in children or adolescents. For the 2.5 mL vial, the maximum human dose of ioflupane, epitomised by the administration of DaTSCAN at the recommended maximum radioactive dose, at the lowest specific activity and at the end of its shelf-life, is 0.325 µg (for the 5 mL vial formulation, the maximum dose is 0.65 µg). A DaTSCAN investigation would require a single administration but it might be repeated, after a period of several months or years in cases where a follow-up is required.

In non-clinical pharmacology and toxicology studies, ratios of animal dose to human dose are based on relative body surface areas. The factors used for these calculations assume a human body weight of 60 kg and are for the mouse, 12.3, for the rat, 6.2, for the rabbit and cynomolgus monkey, 3.1 and for the dog 1.8. The maximum human mass dose of ioflupane is 0.325 µg/60 kg (5.4 ng/kg) calculated for the 2.5 mL formulation of DaTSCAN. All safety margins shown below are body surface area adjusted and are used to relate the nonclinical dose to the human equivalent dose. For the 5 mL formulation, divide these values by 2.

In vitro and in vivo primary pharmacology studies demonstrate that the efficacy of the product is due to the selective affinity of ioflupane for the pre-synaptic dopamine transporter (DAT), the main localization of which is on the dopaminergic axon terminals found in greatest concentration in the striatum. Because the DAT distribution in the central nervous system coincides with dopaminergic innervation, ioflupane (^{123}I) can be used for neuroimaging as an in vivo marker of functional dopaminergic systems, specifically for detecting loss of functional nigrostriatal dopaminergic neurons in patients with dementias and/or movement disorders.

The affinity of ioflupane for the DAT has been demonstrated in vitro (in studies from different laboratories using a range of transporter sources). In vivo studies in a range of animal species

have confirmed the localization of the radiolabelled ioflupane molecule in the striatum of normal animals. More importantly it has been adequately demonstrated in well-established animal models that the degree of striatal uptake, and the associated target-to-background ratios (reflected in *in vivo* ioflupane (^{123}I) SPECT images) correlate well with the extent of the dopaminergic deficiency (reflected in in-life behavioural indicators and ex vivo histochemistry and histopathology).

Pharmacokinetic studies have demonstrated a good correlation between distribution, metabolism and excretion in animal species and humans, leading to the acceptability of safety pharmacology and toxicity data obtained from a number of animal species. The pharmacokinetics of ioflupane (^{123}I) lead to radiation dosimetry estimates in line with those for other diagnostic radiopharmaceuticals

Safety pharmacology studies have demonstrated that, at doses greatly in excess of those that would be used clinically, ioflupane elicits the expected effects, which are considered cocaine-like. Functional observation battery studies in rats found no significant observations at doses up to 1600 times the maximum human dose. In the second study, one rat (of 6) in the high dose group (100 µg/kg; 2700 times the maximum human dose) showed signs of enhanced stereotypical behaviours, but no other effects on spontaneous locomotor activity, motor co-ordination or body temperature were observed in any animals.

Despite the demonstration of a dose response curve in an in vitro assay, in in vivo cardiovascular/respiratory studies in dogs only slight and transient elevated diastolic, systolic and mean arterial blood pressure, heart rate and respiratory rate was noted at doses 9000 times the maximum human dose. The no-observed-adverse-effect-level (NOAEL) in these studies was 10 µg/kg (900 times the maximum human dose).

Toxicity studies have been performed in the rat, as the rodent species, and in the rabbit, dog and cynomolgus monkey, as the non-rodent species. All species have proven suitability for evaluation of toxic potential and have been used previously in the assessment of the toxicity of radiopharmaceuticals.

In acute studies the highest doses of ioflupane that caused no deaths or signs of toxicity were 1 mg/kg in rats, 0.06 mg/kg in rabbits, 0.3 mg/kg in dogs and 0.1 mg/kg in cynomolgus monkeys. These doses are respectively approximately 27000, 3200, 30000 and 5500 times the maximum human dose.

In the repeated-dose studies the NOAEL was 0.6 mg/kg/day in rats and rabbits, and 1 µg/kg/day in dogs (16000, 32000 and 100 times the maximum human equivalent dose). Ioflupane was tested in 5 different assays for genotoxicity and was not found to be mutagenic in any of these test systems.

Nonclinical data reveal no special hazard for humans based on studies on safety pharmacology, single and repeated dose toxicity (dosing up to 14 consecutive days), genotoxicity, local

tolerance and irritation. In the nonclinical studies, doses significantly higher than those relevant for clinical use have been administered.

Based on the nonclinical programme and subsequent use in clinical practice with good safety records, no additional nonclinical studies are considered necessary. The key safety findings for DaTSCAN from nonclinical studies are presented in Table 2.

Table 2 Key safety findings (from nonclinical studies) relevant to human usage

Key Safety Findings (from nonclinical studies)	Relevance to human usage
Toxicity	
Acute Toxicity Potential toxicity after a single iv administration of ioflupane was examined in rats, rabbits, dogs and cynomolgus monkeys. From 2 separate rat studies the most conservative NOAEL (10 µg/kg) was 300 times the maximum human dose. In rabbits no effects were observed following a single dose of 60 µg/kg (3200 times the maximum human equivalent dose). In dogs, the NOAEL was considered 1 µg/kg (100 times the maximum human dose). In cynomolgus monkeys, a NOAEL of 0.3 µg/kg (18 times the maximum human dose) was determined.	**None:** Doses with clinical signs are deemed to be significantly higher than a clinical dose and thus present no concerns. Safety concern refuted by nonclinical studies
Repeat dose studies Four 14-day repeated-dose intravenous toxicity studies have been performed in rats, rabbits and dogs. The doses used in the rat and rabbit studies were based on the results of 7-day dose range finding studies. In rats, the most conservative NOAEL was 10 µg/kg/day (300 times the maximum human dose). In rabbits, a NOAEL of approximately 32000 times the maximum human dose (0.6 mg/kg/day) was determined. In dogs, the NOAEL was 1 µg/kg/day (100 times the maximum human dose.	**None**: Safety concern refuted by nonclinical studies.
Genotoxicity Three in vitro and 2 in vivo tests for genotoxicity have been performed according to good laboratory practice (GLP) and ICH guidance. Ioflupane was determined to be non-mutagenic in a reverse mutation assay (Ames) in *S. typhimuriu*. and in an in vitro gene mutation assay in mouse lymphoma cells. Ioflupane was considered to be non-clastogenic in an in vitro chromosomal aberration assay in human lymphocytes In 2 in vivo micronucleus studies in mice injected intravenously with a single dose of ioflupane of up to 20 mg/kg or on 2 consecutive days with doses up to	**None**: Safety concern refuted by nonclinical studies.

Table 2 Key safety findings (from nonclinical studies) relevant to human usage

Key Safety Findings (from nonclinical studies)	Relevance to human usage
300 µg/kg there were no statistically significant increases in the frequency of micronuclei in any test groups at any sampling time in either study.	
Local toxicity Studies were performed to assess the tolerance of rats and rabbits to intravenous administration of the ethanolic acetate buffer vehicle. The ethanolic acetate buffer was well tolerated systemically although slight discomfort during the administration procedure was evident with some signs of reaction at the injection site. Any lesions observed were considered to be the result of mechanical trauma caused by the injection technique rather than intolerance to the test item.	**None**: Safety concern refuted by nonclinical studies
Safety Pharmacology	
Cardiovascular/Respiratory In vitro study to assess the potential of ioflupane to inhibit hERG tail current, observed a no-effect concentration of 0.02 µM (70 times the calculated maximum predicted human plasma concentration assuming an average human plasma volume of 3 L). Two cardiovascular/respiratory studies have been performed in conscious telemeterised dogs to evaluate cardiovascular and respiratory effects induced by ioflupane. In the first study, the intravenous administration of ioflupane at doses up to 6.0 µg/kg (550 times the maximum human dose) did not cause any morbidity or deaths and did not induce statistically significant changes in any of the measured parameters (including QT interval). In the second GLP dog study, the only effects observed were in the high dose group (100 µg/kg; approximately 9000 times the maximum human dose) and comprised a slightly and transiently elevated diastolic, systolic and mean arterial blood pressure, heart rate and respiratory rate. There were no recorded changes in the other dose groups for these parameters. No other effects were observed. The NOAEL was 10 µg/kg (900 times the maximum human equivalent dose).	**None**: Doses with clinical signs are deemed to be higher than a clinical dose and thus present no concerns. Safety concern refuted by nonclinical studies

Table 2 Key safety findings (from nonclinical studies) relevant to human usage

Key Safety Findings (from nonclinical studies)	Relevance to human usage
Central Nervous System Functional observation battery studies in rats found no significant observations at doses up to 60 µg/kg or 1600 times the maximum human dose. In the second study, one rat (of 6) in the high dose group (100 µg/kg; 2700 times the maximum human dose) showed signs of enhanced stereotypical behaviours, but no other effects on spontaneous locomotor activity, motor co-ordination ("rota-rod" performance) or body temperature were observed in any animals.	**None:** Doses with clinical signs are deemed to be higher than a clinical dose and thus present no concerns. Safety concern refuted by nonclinical studies.

Summary of the findings from nonclinical testing

Safety concerns:

Important identified risks (confirmed by clinical data):

None identified.

Important potential risks (not refuted by clinical data or which are of unknown significance):

None identified.

Missing information:

There is no information regarding pregnancy, lactation and fetotoxicity and the use of DaTSCAN in the nonclinical data.

Part II: Module SIII - Clinical trial exposure

GE Healthcare has sponsored clinical trials concerning DaTSCAN to evaluate its efficacy and safety. Cumulatively, GE Healthcare has sponsored a total of 10 studies since the international birth date of DaTSCAN and up to 27 July 2017 where a total of 1,486 subjects have been enrolled. Of these, 1,180 subjects received DaTSCAN, and were analysed in the safety population. The first study was initiated in 1996, while the most recent study was completed in 2012. One of the studies was a Phase I study, two were Phase II studies, four were Phase III studies, one was Phase III/IV and two were Phase IV studies. There are currently no on-going studies involving DaTSCAN.

Table 3 presents the numbers of subjects enrolled in company sponsored clinical trials. In total, 1486 subjects were enrolled.

Table 3 Cumulative Subject Exposure from Clinical Studies

Treatment	Number of Subjects
DaTSCAN	1,180
Not DaTSCAN	306
Comparator	Unknown
Placebo	Unknown

Demographic data such as gender, race, indication and age group were collected for all subjects for all conducted studies as shown below in Table 4, Table 5, Table 6 and Table 7. One of the studies conducted by GE Healthcare included only healthy volunteers to examine the biodistribution, safety and tolerability of DaTSCAN. Subsequent studies have focused on the use of DaTSCAN in relation with Parkinson, essential tremor, dementia with Lewy Body and Alzheimer's disease as shown in Table 4. The racial background for each subject was collected for all 10 studies. As shown in Table 6, the majority of exposed subjects was Caucasian (97%), while the second largest group was Hispanic (1.4%). Demographic data for the 1,180 subjects included in the safety population are available in [Grosset et al. 2014].

Table 4 Cumulative subject exposure to DaTSCAN from completed clinical trials by indication

Indication	All subjects enrolled
Parkinsonian syndrome and/or essential tremor	913
Dementia with Lewy Body and/or Alzheimer's disease	513
Healthy volunteers	60
Other	0
Unknown	0
Grand total (all indications)	**1,486**

Table 5 Cumulative subject exposure to DaTSCAN from completed clinical trials by gender

Gender	Number of subjects
Male	840
Female	645
Unknown	1
Total number of subjects	**1,486**

Table 6 Cumulative subject exposure to DaTSCAN from completed clinical trials by racial group

Race	Number of subjects
Caucasian	1,443
Black	10
Asian/Oriental	8
Hispanic	20
Other	1
Unknown	4

Table 6 Cumulative subject exposure to DaTSCAN from completed clinical trials by racial group

Race	Number of subjects
Total number of subjects	**1,486**

Table 7 Cumulative subject exposure to DaTSCAN from completed clinical trials by age group

Age range (years)	Number of subjects
10-19	2
20-29	2
30-39	18
40-49	86
50-59	224
60-69	444
70-79	540
80-89	161
90-99	3
Unknown	6
Total	**1,486**

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

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

Sensitivity to any component in formulation including iodine

Reason for exclusion

Prevention of potential hypersensitivity reaction.

Is it considered to be included as missing information? No

Rationale

Hypersensitivity is an already identified risk for ioflupane (^{123}I), and is addressed in both the Company Core Safety Information (CCSI) and SmPC for DaTSCAN.

Women of child-bearing potential not using adequate birth control, who are pregnant or planning to become pregnant

Reason for exclusion

No pregnant women were studied, due to potential harm to the foetus from radioactivity. This is standard practice in clinical studies of radiopharmaceuticals.

Is it considered to be included as missing information? No

Rationale

DaTSCAN is contraindicated in pregnancy.

Women who are breast-feeding

Reason for exclusion

No breast-feeding women were studied, due to potential harm to nursing infant from radioactivity. This is standard practice in clinical studies of radiopharmaceuticals.

Is it considered to be included as missing information? No

Rationale

It is not known if ioflupane (^{123}I) is excreted in human milk, however the potential risk is already identified for DaTSCAN, and is addressed in both the CCSI and SmPC for DaTSCAN.

Patients on drugs known to interfere with binding of ioflupane (^{123}I)

Reason for exclusion

Concomitant medication that bind to the dopamine transporter with high affinity may compete with ioflupane (^{123}I) binding, and thus, cause false positive imaging results.

Is it considered to be included as missing information? No

Rationale

The risk of other drugs interfering with ioflupane (^{123}I) uptake is already known and is addressed in both the CCSI and SmPC for DaTSCAN.

Patients with significant renal disease or hepatic disease

Reason for exclusion

At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine. There is a rapid initial clearance of circulating ioflupane, followed by a slow clearance as ioflupane is released from other compartments. Less than 14% of the injected dose is eliminated via the faeces.

Is it considered to be included as missing information? No

Rationale

Owing to the nature of nuclear imaging and the very small effective administered (dose is less than 20 mSv), no impact is expected on either efficacy or safety in patients with significant renal disease or hepatic disease. The potential risk for increased radiation exposure is addressed in both the CCSI and SmPC for DaTSCAN, which includes a recommendation to avoid administering DaTSCAN to patients with moderate to severe renal impairment.

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.

No relevant limitations of the clinical database have been identified. The size of the clinical trial database allows for detection of adverse drug reactions (ADRs) with a frequency greater that 1:393 (based on the "rule of three"). Other potential limitations are not considered to be of relevance. Table 8 discusses limitations of ADR detection in the DaTSCAN clinical trial programme.

Table 8 Limitations of ADR detection

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
which are rare	Approx. 1,180 patients were exposed over the entire clinical trial program.	Adverse drug reactions occurring with a frequency greater than 1 in 393 could be detected in a patient population of 1,180.
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

Not relevant because DaTSCAN 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 9 presents exposure in the populations of patients that were excluded or under-represented when the safety of DaTSCAN was studied in the clinical development programme, sorted by indication.

Table 9 Exposure of special populations included or not in clinical trial development programmes, sorted by indication

Type of special population	Exposure in neurologic indications
Pregnant and breastfeeding women	Not included in the clinical development program
Patients with hepatic impairment	4
Patients with renal impairment	46
Patients with cardiovascular impairment	328
Immunocompromised patients	24
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms:	Not included in the clinical development program
Other	Not included in the clinical development program

Part II: Module SV - Post-authorization experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The total number of DaTSCAN vials sold worldwide since first marketing authorization for in July 2000 is 1,596,254. It is assumed that one vial is used for a single patient. Thus, it is estimated that approximately 1.6 patients have received DaTSCAN since its launch.

Table 10 presents an overall, cumulative estimation of patient exposure, based upon data obtained from 28 July 2000 to 31 December 2019. Data regarding indication, dose, sex and age was not available.

Market research suggests that DaTSCAN is used for certain off-label indications (e.g. brain cancer, numbness, paralysis, weakness, altered taste sensation etc.). The marketing authorisation holder is not aware of safety concerns related to off-label use.

SV.1.2 Exposure

Table 10 Cumulative patient exposure to DaTSCAN from July 2000 to 31 December 2019

Indication	**Sex**			**Age (years)**				**Region**				
All indications	Male	Female	Unknown	2 to ≤16	16 to 65	>65	Unknown	Europe	Asia-Pacific	America	EAGM	Unknown
	Unk	Unk	1,6 mill.	Unk	Unk	Unk	1,6 mill	659,930	335,378	112,274	464	489,208

EAGM: Eastern and African Growth Markets; LATAM: Latin America; Unk: Unknown

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

Potential for misuse for illegal purposes

It is unlikely that the product could be misused for illegal purposes such as a recreational drug or to facilitate assault, since DaTSCAN is available through prescription only, and is administered by health-care professionals.

Part II: Module SVII - Identified and potential risks

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

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

Reason for not including an identified or potential risk 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 are known risks that require no further characterisation and no additional risk minimisation measures. The risks are followed up via routine pharmacovigilance, i.e. through signal detection and adverse reaction reporting, and risk minimisation messages are provided in the product information.

Hypersensitivity

According to approved product information, the possibility of hypersensitivity including anaphylactic/anaphylactoid reactions should always be considered. Severe hypersensitivity reactions cannot be prevented, but this risk can be readily mitigated by early recognition of anaphylactoid reactions and appropriate symptomatic treatment.

A cumulative search in the global adverse event database (GAED) identified 23 cases of hypersensitivity and hypersensitivity-like reactions. Six (6) of the cases were serious, and all patient were reported to have recovered:

- Three (3) serious cases reported cutaneous hypersensitivity reactions like rash, pruritus or erythema that started within minutes to same day unknown latency following DaTSCAN administration. All cases were reported to have resolved following treatment.
- One (1) serious case of throat and neck swelling within 1 hour following DaTSCAN administration, although reported to be able to breath and swallow without difficulty. The patient was reported to have recovered within 6 hours following treatment.

- Two (2) cases were assessed to be unrelated to DaTSCAN administration
  - In one of the serious cases, an 83-year-old male patient reportedly experienced anaphylactic shock approximately 3 hours following DaTSCAN. The patient experienced anxiety, rough breathing, drop in oxygen saturation, discoloration of lips and reduced blood pressure. He was treated with oxygen and IV fluid hydration. MAH attributes the event to most likely dehydration from diuretics within the setting of underlying cardiovascular disease and the vasodilatory properties from concomitant medications including candesartan, azosemide [redacted], spironolactone (Aldactone A), nicorandil [redacted], diltiazem hydrochloride and nitroglycerine causing hypotension. Based on the delayed onset (only 5% of DaTSCAN remains in whole blood 5 minutes post-injection), the treatment administered and the patients underlying conditions and concomitant medications, the MAH considers that the event to be unlikely due to the use of DaTSCAN.
  - One case reported from a non-GEHC sponsored study, concerned infusion related reaction presenting as orthostatic hypotension that occurred more than 3 months after DaTSCAN administration. It was reported as not related to DaTSCAN, instead the reaction was considered related to the investigational drug in the study.

The 17 non-serious cases concerned mild to moderate hypersensitivity reactions, or symptom consistent with hypersensitivity.

Hypersensitivity is an adverse reaction with potential serious clinical consequences but is occurring with a low frequency and is therefore considered acceptable in relation to the benefit of DaTSCAN imaging. The potential risk of hypersensitivity reactions is adequately addressed in both the CCSI and SmPC section 4.4 for DaTSCAN. They also include recommendations to have advanced life support facilities readily available when administering DaTSCAN. No additional regulatory actions are considered required. No additional risk minimization activities are proposed.

Exposure to ionising radiation

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations, the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred. For most diagnostic investigations using a nuclear medicine procedure, the effective dose is less than 20 mSv. The radiation dose associated with use of DaTSCAN is comparable to that for other imaging modalities, approximately 4.63 mSv for an adult when the maximal recommended activity of 185 MBq is administered.

A cumulative search in the GAED did not identify case reports concerning System Organ Class (SOC) Congenital, familial and genetic disorders or High Level Term Radiation injuries.

Six cases reports were identified within SOC Neoplasms benign, malignant and unspecified (including cysts and polyps).

- One serious case from post-marketing experience is a physician report from [redacted] involving a patient (age and sex not reported) who experienced thyroid cancer six (6) months after administration of DaTSCAN for an unspecified indication. Treatment details were not reported. Concurrent medical conditions/past medical history and concomitant medications were not reported. Limited information was provided and the case does therefore not contribute with new information about exposure to ionising radiation.
- The remaining 5 serious cases were reports from clinical trials, and all events were considered unrelated to the study drug, according to the reporting investigators.

The clinical experience with this agent indicates that the risks associated with this procedure are far outweighed by the diagnostic information it provides. The theoretical risk of cancer induction and a potential for development of hereditary defects due to ionizing radiation are addressed in section 4.8 of both the CCSI and SmPC for DaTSCAN. In addition, the SmPC section 4.4 for DaTSCAN includes a recommendation to administer as low as reasonably achievable activity to obtain the required diagnostic information. No additional regulatory actions are considered required. No additional risk minimization activities are proposed.

Possibility of adverse reactions in patients suffering from alcoholism, liver disease and epilepsy due to an excipient ethanol

DaTSCAN, 74 MBq/ml solution for injection contains 39.5 g/L ethanol which can be harmful for those suffering from alcoholism, and should be taken into account in high-risk groups such as patients with liver disease or epilepsy.

Cumulatively, no case reports concerning adverse reactions in patients suffering from alcoholism, liver disease and epilepsy due to an excipient ethanol have been identified by the MAH.

The actually injected amount of alcohol in the product is very small; up to 197 mg per dose, which is equivalent to 5 ml beer or 2 ml wine. The potential risk of adverse reactions due to the excipient alcohol is already well-known to health professionals, and appropriate language is included in SmPC section 4.4 for DaTSCAN. No additional regulatory actions are considered required. No additional risk minimization activities are proposed.

Possibility of adverse effects in patients with significant hepatic or renal impairment

At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine. There is a rapid initial clearance of circulating ioflupane, followed by a slow clearance as ioflupane is released from other compartments. It is a theoretical possibility that patients with renal and/or hepatic impairment experience reduced elimination of ioflupane (^{123}I), and

patients with significant renal disease or hepatic disease were therefore excluded from clinical studies.

A cumulative search in the GAED did not identify any relevant case reports concerning adverse effects in patients with significant hepatic or renal impairment have been identified by the MAH.

In the absence of data of use of DaTSCAN in patients with significant hepatic or renal impairment, it is not recommended to use in patients with moderate or severe renal impairment, or hepatic impairment. The potential risk in patients with hepatic or renal impairment is addressed in section 4.4 of both the CCSI and SmPC for DaTSCAN. No additional regulatory actions are considered required. No additional risk minimization activities are proposed.

Possibility of adverse effects in pregnant and lactating women

Administration of 185 MBq of ioflupane (^{123}I) results in an absorbed dose to the uterus of 3.0 mGy. It is not known whether ioflupane (^{123}I) is excreted in human milk. In theory, low levels of ionising radiation may have the potential to lead to cancers and hereditary defects through irreparable damage of nuclear DNA resulting in mutations of somatic and germ cells, although, radiation doses under 50 mGy generally have not been associated with congenital anomalies [Yoon and Slesinger. 2020].

Cumulatively, no case reports concerning adverse effects in pregnant and lactating women have been identified by the MAH.

Considering the target population and the absence of case reports, the risk of adverse effects in pregnant and lactating women is low. Regardless of this, use of DaTSCAN during pregnancy is contraindicated in the SmPC, and the potential risk in this population is addressed in section 4.6 of both the CCSI and SmPC for DaTSCAN. No additional regulatory actions are considered required. No additional risk minimization activities are proposed.

Potential uptake of (^{123}I) by the thyroid gland

Blockade of the thyroid gland is a measure routinely employed in departments of nuclear medicine to reduced undesirable or unintended thyroid uptake of radioactive iodide and hence to reduce the radiation dose to the thyroid. It is performed particularly in circumstances where the adventitious absorbed dose, and hence the risk, to the thyroid might be high.

The CCSI and SmPC section 4.2 for DaTSCAN indicates that patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine, for example by oral administration of approximately 120 mg potassium iodide 1 to 4 hours prior to injection of DaTSCAN.

For a 185 MBq administration of DaTSCAN, the maximum absorbed radiation dose to the unblocked thyroid gland is estimated to be 39.9 mGy. This includes contributions from the biodistribution and thyroid uptake of the maximum permissible content of radiochemical (6%

free iodide ^{123}I) and radionuclidic (0.1% ^{125}I) impurities. The radiation dose to the thyroid can be reduced to 1.7 mGy by pre-administration thyroid blockade using one of the protocols recommended in the approved labeling. In addition to the very low levels of radionuclidic impurities in DaTSCAN, [^{123}I]ioflupane is not de-iodinated *in vivo* [Baldwin et al. 1995] and the amount injected is very low, [Tanaka et al. 1999], iodine-123 has a physical half-life of 13.2 hours and blood clearance is rapid.

The blocking effect of stable iodide lasts for many days [Verger et al. 2001], thus there is no need for a second administration of a blocking agent 12-24 hours after DaTSCAN administration. Considering that ^{123}I is a gamma emitter (principal radiation emission of 159 keV, 83% of abundance) with a short half-life (13.2 hours), no significant thyroid effects are expected.

The potential risk of thyroid effects is already well-known to health professionals and is included in scientific guidelines, such as [Darcourt et al. 2010], [Djang et al. 2012], [EANM/SNMMI guideline 2020], and does not require additional pharmacovigilance activities or additional risk minimisation measures.

A search in the GAED identified one spontaneous case report when searching for SMQ thyroid dysfunction (broad) after [^{123}I]ioflupane administration. This non-serious case concerned a product complaint of "increased thyroid uptake (of ^{123}I)" after DaTSCAN administration. The patient was pre-treated with a blocking agent, and the images were diagnostic. No adverse events were reported. A quality investigation did not identify any quality issues with the batch documentation.

In conclusion, there have been no reports following use of DaTSCAN, suggestive of any short- or long-term effects on the thyroid that could be attributed to uptake of radioactive iodide nuclides ^{123}I or ^{125}I.

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

None.

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

Not applicable.

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

No safety information for DaTSCAN has been characterized as a safety concern relevant for inclusion in the RMP for DaTSCAN.

Part II: Module SVIII - Summary of the safety concerns

No safety information for DaTSCAN has been characterized as a safety concern relevant for inclusion in the RMP for DaTSCAN.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

None proposed.

Other forms of routine pharmacovigilance activities

None proposed.

III.2 Additional Pharmacovigilance Activities

There are no on-going or planned additional pharmacovigilance studies/activities in the pharmacovigilance plan.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable since there are no on-going or planned additional pharmacovigilance studies/activities in the pharmacovigilance plan.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This section is not applicable to DaTSCAN as no post-authorisation efficacy studies are planned.

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

Risk Minimisation Plan

This section is not applicable since there are no important identified or potential risks, or missing information, identified for DaTSCAN.

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 DaTSCAN (ioflupane (^{123}I))

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

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

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

I. The medicine and what it is used for

DaTSCAN is authorised for detecting loss of functional dopaminergic neuron terminals in the striatum:

- In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.
- In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease. DaTSCAN is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.

DaTSCAN contains ioflupane (^{123}I) as the active substance and it is given by intravenous injection or infusion.

Further information about the evaluation of DaTSCAN's benefits can be found in DaTSCAN'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/datscan.

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

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 DaTSCAN 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 DaTSCAN. 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);

II.B Summary of important risks

This section is not applicable since there are no important identified or potential risks, or missing information, identified for DaTSCAN.

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 DaTSCAN.

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

There are no studies required for DaTSCAN.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES

Not applicable.