1. NAME OF THE MEDICINAL PRODUCT

DaTSCAN 74 MBq/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains ioflupane (^{123}I) 74 MBq at reference time (0.07 to 0.13 μg/ml of ioflupane).

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.

Excipient(s) with known effect
This medicinal product contains 39.5 g/l ethanol.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DaTSCAN is a radiopharmaceutical indicated for striatal dopamine transporter visualisation using single photon emission computed tomography (SPECT) brain imaging to assist evaluation:

- In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from tremor due to 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 is an adjunct to other diagnostic evaluations.

4.2 Posology and method of administration

Prior to administration appropriate resuscitation equipment should be available.

DaTSCAN should only be used in adult patients referred by physicians experienced in the management of movement disorders and/or dementia. DaTSCAN should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides within a designated clinical setting.

Posology

Clinical efficacy has been demonstrated across the range 111 to 185 MBq. Do not exceed 185 MBq and do not use when the activity is below 110 MBq.

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.

Special populations

Renal and hepatic impairment
Formal studies have not been carried out in patients with significant renal or hepatic impairment. No data are available (see section 4.4).

Paediatric population
The safety and efficacy of DaTSCAN in children aged 0 to 18 years has not been established. No data are available.

Method of Administration
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.

SPECT imaging should take place between three and six hours post-injection. Images should be acquired using a gamma camera fitted with a high-resolution collimator and calibrated using the 159 keV photopeak and a ± 10% energy window. Angular sampling should preferably be not less than 120 views over 360 degrees. For high resolution collimators the radius of rotation should be consistent and set as small as possible (typically 11-15cm). Experimental studies with a striatal phantom, suggest that optimal images are obtained with matrix size and zoom factors selected to give a pixel size of 3.5-4.5 mm for those systems currently in use. A minimum of 500k counts should be collected for optimal images. Normal images are characterised by two symmetrical crescent-shaped areas of equal intensity. Abnormal images are either asymmetric or symmetric with unequal intensity and/or loss of crescent.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

If hypersensitivity reactions occur, the administration of the medicinal product must be discontinued immediately and, if necessary, intravenous treatment initiated. Resuscitative medicinal products and equipment (e.g. endotracheal tube and ventilator) have to be readily available.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and the appropriate licences of the local competent official organisations.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result.

Formal studies have not been carried out in patients with significant renal or hepatic impairment. In the absence of data, DaTSCAN is not recommended in cases of moderate to severe renal or hepatic impairment.

This medicinal product contains 39.5 g/l (5% volume) ethanol (alcohol), up to 197 mg per dose, equivalent to 5 ml beer or 2 ml wine. Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

The ioflupane within DaTSCAN binds to the dopamine transporter. Drugs that bind to the dopamine transporter with high affinity may interfere with the image obtained following DaTSCAN administration. These potentially interfering drugs consist of: amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, selegiline, and sertraline. Selective serotonin reuptake inhibitors (paroxetine and citalopram) may increase or decrease ioflupane binding to the dopamine transporter. Whether discontinuation of these drugs prior to DaTSCAN administration may minimise the interference with a DaTSCAN image is unknown. The impact of dopamine agonists and antagonists upon DaTSCAN imaging results has not been established.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Where it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed pregnant until proven otherwise. Where uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving satisfactory imaging. Alternative techniques which do not involve ionising radiation should be considered.

Pregnancy
Animal reproductive toxicity studies have not been performed with this product. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Administration of 185 MBq of ioflupane (^{123}I) results in an absorbed dose to the uterus of 3.0 mGy. DaTSCAN is contraindicated in pregnancy (see section 4.3).

Breastfeeding
It is not known whether ioflupane (^{123}I) is excreted in human milk. Before administering a radioactive medicinal product to a breast-feeding mother, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast-feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of radioactivity in breast milk. If administration is considered necessary, breast-feeding should be interrupted for 3 days and substituted by formula feeding. During this time, breast milk should be expressed at regular intervals and the expressed feeds should be discarded.

Fertility
No fertility studies have been performed. No data are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

The frequencies of adverse reactions are defined as follows:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects are recognized for DaTSCAN:

Skin and subcutaneous tissue disorders
Not known: Erythema, Pruritus, Rash, Urticaria, Hyperhidrosis

Respiratory, thoracic and mediastinal disorders
Not known: Dyspnea

Immune system disorders
Not known: Hypersensitivity

Metabolism and nutrition disorders
Uncommon: Appetite increased

Nervous system disorders
Common: Headache
Uncommon: Dizziness, formication (paraesthesia), dysgeusia

Ear and labyrinth disorders
Uncommon: Vertigo

Gastrointestinal disorders
Uncommon: Nausea, dry mouth
Not known: Vomiting

Vascular disorders
Not known: Blood pressure decreased

General disorders and administration site conditions
Uncommon: Injection site pain (intense pain *or burning sensation* following administration into small veins)
Not known: Feeling hot

Updated effective dose for the maximum recommended activity of 185 MBq

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 4.63 mSv when the maximal recommended activity of 185 MBq is administered these adverse events are expected to occur with a low probability.

4.9 Overdose

In cases of overdose of radioactivity, frequent micturition and defaecation should be encouraged in order to minimise radiation dose to the patient. Care should be taken to avoid contamination from the radioactivity eliminated by the patient using such methods.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical central nervous system,
ATC code: V09AB03.

Due to the low quantities of ioflupane injected, pharmacological effects are not expected following

intravenous administration of DaTSCAN at the recommended dosage.

Mechanism of action

Ioflupane is a cocaine analogue. Studies in animals have shown that ioflupane binds with high affinity to the presynaptic dopamine transporter and so radiolabelled ioflupane (^{123}I) can be used as a surrogate marker to examine the integrity of the dopaminergic nigrostriatal neurons. Ioflupane also binds to the serotonin transporter on 5-HT neurons but with lower (approximately 10-fold) binding affinity.

There is no experience in types of tremor other than essential tremor.

Clinical efficacy

Clinical studies in patients with Parkinsonian Syndromes (PS)

The safety and efficacy of DaTSCAN were evaluated in two multicentre, single-arm studies (Study 1

and Study 2) that evaluated 284 adult patients with tremor. In the studies, DaTSCAN image outcomes were compared to a reference clinical diagnostic standard of "PS" or “non-PS”. The reference clinical diagnostic standard for "PS" consisted of the following diagnoses: Parkinson’s disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). These three conditions have been associated with dopaminergic neurodegeneration and DaTSCAN imaging was not designed to distinguish among the conditions. The reference clinical diagnostic standard for "non-PS" consisted of an essential tremor (ET) diagnosis or other non-PS diagnosis. Three to 6 hours after DaTSCAN administration, subjects underwent SPECT imaging with a variety of multi-headed cameras or a multi-detector single-slice systems. The median administered activity evaluated in clinical studies was 173 MBq (4.7 mCi) [range, 88 to 287 MBq (2.4 to 7.8 mCi)].

DaTSCAN images were evaluated by readers blinded to clinical information. Study 1 readers had no other role in patient assessment; Study 2 readers included site investigators. The reference clinical diagnostic standards were the clinical diagnoses established by a consensus panel of movement disorder specialists that evaluated data inclusive through 36 months of follow-up (Study 1) or the investigator-determined baseline clinical diagnosis (Study 2). Study 1 consisted of patients with early features of Parkinsonism; patients with features suggestive of MSA or PSP were excluded. Study 2 consisted of patients with clinically established diagnosis of PS (PD, MSA, PSP) or ET.

Among the 102 subjects (99 patients and 3 healthy subjects) in Study 1, 44% were female, 41% were aged 65 or over and all were Caucasian; among the 200 subjects (185 patients and 35 healthy subjects) in Study 2, 38% were female, 46% were aged 65 or over and 98% were Caucasian. Among the patients in Study 1, the baseline clinical diagnoses consisted of: probable PD (44%), possible PD (31%), “benign” PD (6%), possible ET (11%), and other diagnoses (7%). Among the patients in Study 2, the baseline clinical diagnoses consisted of: PD (70%), ET (15%), MSA (10%), and PSP (5%).

Table 1 shows the sensitivity and specificity of the DaTSCAN image results with the reference clinical diagnostic standard. Sensitivity represents the percent of patients with abnormal DaTSCAN images among all the patients with a clinical diagnostic reference standard of PS. The specificity represents the percent of patients with normal DaTSCAN images among the patients with a non-PS clinical diagnostic reference standard.

Table 1 Sensitivity and specificity for Studies 1 and 2

	Sensitivity (95 % CI) (% subjects with an abnormal DaTSCAN image among patients with PS)	**Specificity (95 % CI) (95 % CI) (% subjects with a normal DaTSCAN image among patients with non-PS**
Study 1 (patients with early signs and/or symptoms of PS, or healthy)		
Reader A, n = 102	77 (66, 87)	96 (83, 100)
Reader B, n = 99	78 (66, 87)	96 (83, 100)
Reader C, n = 101	79 (67, 87)	96 (83, 100)
Study 2 (patients with established diagnoses of PS, ET or healthy)		
Reader A, n = 220	93 (88, 97)	94 (84,98)
Reader B, n = 220	97 (93, 99)	81 (69,90)
Reader C, n = 220	96 (92, 99)	92 (82,97)
Reader D, n = 220	92 (87, 96)	97 (89,100)
Reader E, n = 220	94 (90, 97)	92 (82, 97)

Clinical studies in patients with dementia with Lewy bodies (DLB).

In a pivotal clinical trial including evaluation of 288 subjects with dementia with Lewy bodies (DLB) (144 subjects), Alzheimer’s disease (124 subjects), vascular dementia (9 subjects) or other (11 subjects), the results of an independent, blinded visual assessment of the DaTSCAN images were compared to the clinical diagnosis as determined by physicians experienced in the management and diagnosis of dementias. Clinical categorisation into the respective dementia group was based on a

standardised and comprehensive clinical and neuropsychiatric evaluation.

Table 2 shows the values for sensitivity and specificity of the DaTSCAN image results with the reference clinical diagnostic standard in determining, i. Probable DLB versus non-DLB, ii. Probable DLB versus Possible DLB and non-DLB and iii. Probable/Possible DLB versus non-DLB. In the main analysis, the positive predictive value ranged from 78.9% to 84.4% and the negative predictive value from 86.1% to 88.7%.

Table 2 Sensitivity and Specificity for DLB

	Sensitivity	**Specificity**
Probable DLB vs non-DLB (primary analysis)		
Reader A, n=216	80% (69, 88)	91% (85, 95)
Reader B, n=216	75% (64, 84)	89% (82, 93)
Reader C, n=217	80% (70, 88)	91% (85, 95)
Probable DLB vs Possible DLB and non-DLB (Sensitivity analysis)		
Reader A, n=273	78% (67, 86)	82% (76, 87)
Reader B, n=272	75% (64, 84)	81% (75, 87)
Reader C, n=274	80% (70, 88)	84% (78, 89)
Probable/Possible DLB vs non-DLB (Sensitivity analysis)		
Reader A, n=273	64% (56, 73)	91% (85, 95)
Reader B, n=272	61% (52, 69)	89 (82, 93)
Reader C, n=274	62% (53, 70)	91% (85, 95)

5.2 Pharmacokinetic properties

Distribution
Ioflupane (^{123}I) is cleared rapidly from the blood after intravenous injection; only 5% of the administered activity remains in whole blood at 5 minutes post-injection.

Organ uptake
Uptake in the brain is rapid, reaching about 7% of injected activity at 10 minutes post-injection and decreasing to 3% after 5 hours. About 30% of the whole brain activity is attributed to striatal uptake.

Elimination
At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine, with faecal excretion calculated at approximately 14%.

5.3 Preclinical safety data

Non-clinical data for ioflupane reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

Studies on reproductive toxicity and to assess the carcinogenic potential of ioflupane have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium acetate
Ethanol
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2.5 ml vial: 7 hours from the activity reference time stated on the label.

5 ml vial: 20 hours from the activity reference time stated on the label.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

2.5 or 5 ml solution in a single colourless 10 ml glass vial sealed with a rubber closure and metal overseal.
Pack size of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning
Normal safety precautions for handling radioactive materials should be observed.

Disposal
After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare Pte Ltd
11 North Buona Vista Drive
#11-07 The Metropolis
Singapore 138589

8. DATE OF REVISION OF THE TEXT

June 2022

9. DOSIMETRY

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.

The estimated absorbed radiation doses to an average adult patient (70 kg) from intravenous injection of ioflupane (^{123}I) are listed below. The values are calculated assuming urinary bladder emptying at 4.8-hour intervals and appropriate thyroid blocking (Iodine-123 is a known Auger electron emitter). Frequent bladder emptying should be encouraged after dosing to minimise radiation exposure.

Target Organ	Absorbed radiation dose μGy/MBq
Adrenals	17.0
Bone surface	15.0
Brain	16.0
Breasts	7.3
Gallbladder wall	44.0
Gastrointestinal tract	
Stomach wall	12.0
Small intestine wall	26.0
Colon wall	59.0
(Upper large intestine wall	57.0)
(Lower large intestine wall	62.0)
Heart wall	32.0
Kidneys	13.0
Liver	85.0
Lungs	42.0
Muscles	8.9
Oesophagus	9.4
Ovaries	18.0
Pancreas	17.0
Red marrow	9.3
Salivery glands	41.0
Skin	5.2
Spleen	26.0
Testes	6.3
Thymus	9.4
Thyroid	6.7
Urinary bladder wall	35.0
Uterus	14.0
Remaining organs	10.0
Effective Dose (μSv/MBq)	**25.0**

The effective dose (E) resulting from administration of 185 MBq of DaTSCAN injection is 4.63 mSv (per 70 kg individual). The above data are valid in normal pharmacokinetic behaviour. When renal or hepatic function is impaired, the effective dose and the radiation dose delivered to organs might be increased.

10 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. See also section 6.6.