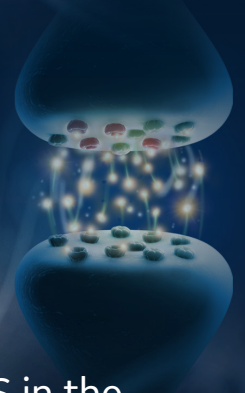


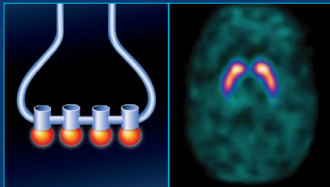


Interpretation of DaTscan results will be based on a normal scan or abnormal scan

Patients with clinical diagnostic uncertainty between PS and ET have a higher likelihood of PS in the presence of abnormal DaT SPECT, and a very low likelihood of PS when the DaT SPECT is normal.¹



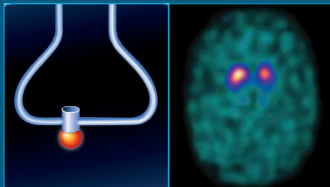
Normal Scan



DaTscan images are interpreted visually, based on the appearance of the striata. [¹²³I] ioflupane binds tightly to the DaT in the brain and allows visualization of striatal DaT.

The brain structures with highest activity of [¹²³I] ioflupane following an injection of DaTscan (in patients with normal DaT distribution) are the left and right caudate and putamen, known collectively as the left and right striata.

Abnormal Scan



Visual review to determine if an image is normal or abnormal is made by assessing the extent (as indicated by shape) and intensity of the striatal signal. Image interpretation does not involve integration of the striatal image appearance with clinical signs and/or symptoms.

PS, parkinsonian syndrome; **ET**, essential tremor.

IMPORTANT SAFETY INFORMATION ABOUT DATSCAN

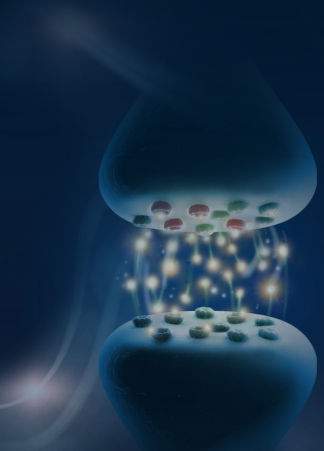
DRUG INTERACTIONS

- Drugs that bind to the dopamine transporter with high affinity may interfere with the DaTscan image. The impact of dopamine agonists and antagonists on DaTscan imaging results has not been established

Please see additional Important Safety Information on the back cover and the enclosed full Prescribing Information.

DaTscan™
Ioflupane I123 Injection

Two principal, multicenter clinical trials that examined the role of [123 I]FP-CIT, DaTscan (I 123 Ioflupane) SPECT, in clinical practice accompanied the NDA for DaTscan²



Study 1 reported on [123 I]FP-CIT, DaTscan (I 123 Ioflupane) SPECT in patients with **early suspected parkinsonism**, comparing baseline scan results to the consensus clinical diagnosis established three years later¹



Study 2 was a trial of DaTscan SPECT in patients with **established diagnoses of parkinsonian syndrome (PS) or essential tremor (ET)**.

Subjects' images were evaluated by blinded reading panel of four experienced nuclear medicine physicians and a neurologist with limited experience assessing [123 I]FP-CIT, DaTscan (I 123 Ioflupane) SPECT scans. Readers rated the images of each case as normal or abnormal¹

ET, essential tremor; **MSA**, multiple system atrophy; **NDA**, new drug application; **PD**, Parkinson's disease; **PS**, parkinsonian syndrome; **PSP**, progressive supranuclear palsy; **SPECT**, single-photon emission computed tomography.

IMPORTANT SAFETY INFORMATION ABOUT DATSCAN)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Radioactive iodine products cross the placenta and can permanently impair fetal thyroid function. Administration of a thyroid blocking agent is recommended before the use of DaTscan in a pregnant woman. All radiopharmaceuticals have potential to cause fetal harm. There are no available data on DaTscan use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Advise pregnant woman of the potential risks of fetal exposure to radiation with the administration of DaTscan
- **Lactation:** Iodine 123 (I 123), the radionuclide in DaTscan, is present in human milk. There is no information on the effects on breastfed infants or on milk. Advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for at least 6 days after DaTscan administration to minimize radiation exposure to a breastfeeding infant
- **Pediatric Use:** The safety and efficacy of DaTscan have not been established in pediatric patients

Please see additional Important Safety Information on the back cover and the enclosed full Prescribing Information.

DaTscan™
Ioflupane I123 Injection



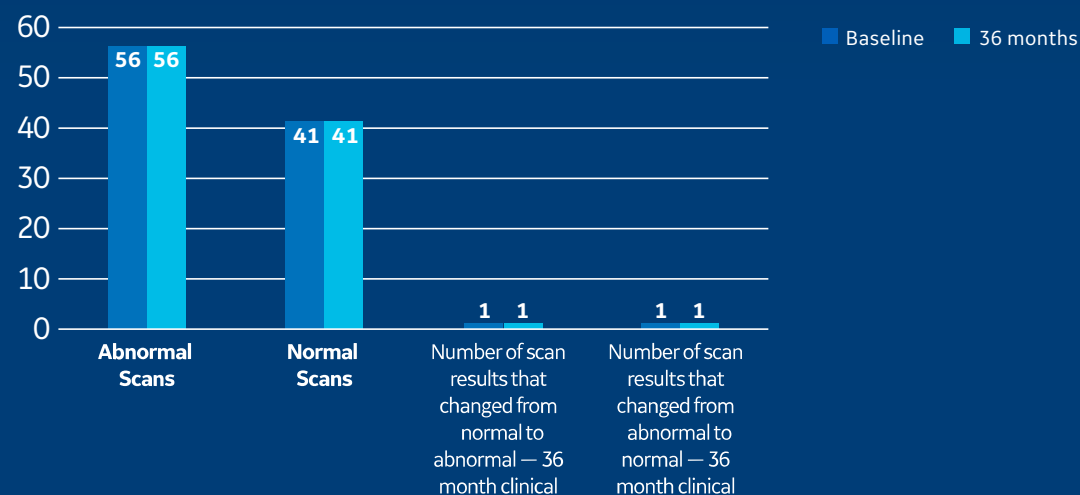
Study 1 reported on [^{123}I]FP-CIT, DaTscan (I 123 Ioflupane) SPECT in patients with **early suspected parkinsonism**, comparing baseline scan results to the consensus clinical diagnosis established three years later.¹

- Clinical diagnosis at 36 months was established by the consensus of two movement disorder specialists who were blind to SPECT findings and working site diagnosis¹
- The clinical diagnosis tended to move toward agreement with the imaging result¹

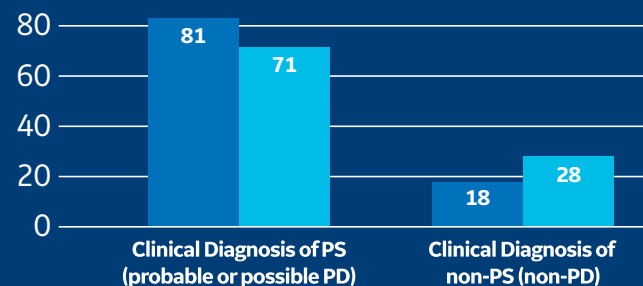


Study 1 included 99 patients with early signs and/or symptoms of PS

Images were evaluated by three independent nuclear medicine physicians who were blind to clinical information



Clinical diagnosis was performed by two movement disorder specialists who were blind to SPECT findings and the working site diagnosis



Adapted from Hauser and Grosset, 2011.

ET, essential tremor; **MSA**, multiple system atrophy; **NDA**, new drug application; **PD**, Parkinson's disease; **PS**, parkinsonian syndrome; **PSP**, progressive supranuclear palsy; **SPECT**, single-photon emission computed tomography.



Study 2 was a trial of DaTscan SPECT in patients with **established diagnoses of parkinsonian syndrome (PS) or essential tremor (ET)**. Subjects' images were evaluated by blinded reading panel of four experienced nuclear medicine physicians and a neurologist with limited experience assessing [¹²³I]FP-CIT, DaTscan (I 123 Ioflupane) SPECT scans. Readers rated the images of each case as normal or abnormal.¹



Study 2 consisted of 185 patients with established diagnoses of PS or ET

Positive and negative percent agreements for Study 2¹

Study 2 (patients with established diagnoses of PS or ET, n = 185)



Positive percent agreement (95% CI) (% patients with an abnormal DaTscan image among patients with PS)



Negative percent agreement (95% CI) (% patients with a normal DaTscan image among patients with non-PS)

	n=158	n=27
Reader A	93 (88, 97)	96 (81, 100)
Reader B	97 (93, 99)	74 (54, 89)
Reader C	96 (92, 99)	85 (66, 96)
Reader D	92 (87, 96)	93 (76, 99)
Reader E	94 (90, 97)	93 (76, 99)

The effectiveness of DaTscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established.

CI, confidence interval; **ET**, essential tremor; **MSA**, multiple system atrophy; **PD**, Parkinson's disease; **PS**, parkinsonian syndrome; **PSP**, progressive supranuclear palsy; **SPECT**, single-photon emission computed tomography.

Safety profile

In clinical trials, no serious adverse reactions related to DaTscan have been reported²

The following adverse reactions have been reported ($\leq 1/100$):

- Headache
- Nausea
- Vertigo
- Dry mouth
- Dizziness

These reactions were of mild to moderate severity.

Hypersensitivity reactions have also been reported following DaTscan administration. The reactions have generally consisted of skin erythema and pruritus and have either resolved spontaneously or following the administration of corticosteroids and antihistamines.

Radiation exposure of 3.94 mSv is less than many CT scans^{2,4}

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of DaTscan cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

References

1. Hauser RA, Grosset DG. [123I]FP-CIT (DaTscan) SPECT brain imaging in patients with suspected parkinsonian syndromes. *J Neuroimaging*. 2011; Mar 16, epub.
2. DaTscan [prescribing information]. Arlington Heights, IL: GE Healthcare; 2020.
3. Colloby SJ, Williams ED, Burn DJ, Lloyd JJ, McKeith IG, O'Brien JT. Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT. *Eur J Nucl Med Mol Imaging*. 2005;32:1176-1185.
4. Health Physics Society. Radiation exposure from medical diagnostic imaging procedures. <http://hps.org/documents/meddiagimaging.pdf>. Accessed January 4, 2016.

mBq, megabecquerel; mCi, millicurie; mSv, millisieverts.

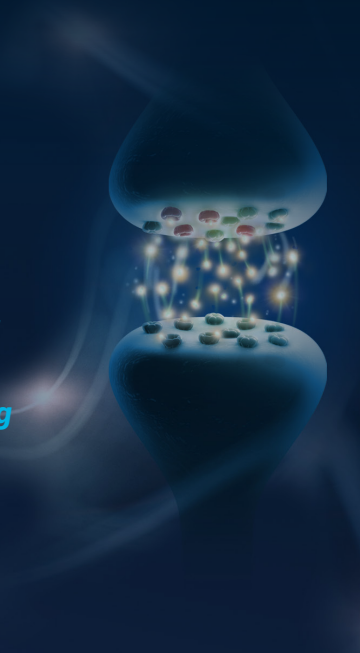
IMPORTANT SAFETY INFORMATION ABOUT DATSCAN

PROCEDURE — Radiation Safety

- DaTscan emits radiation and must be handled with safety measures to minimize radiation exposure to clinical personnel and patients

Please see additional Important Safety Information on the back cover and the enclosed full Prescribing Information.

DaTscan™
Ioflupane I123 Injection



PRODUCT INDICATIONS AND USE

DaTscan™ (Ioflupane I 123 Injection) is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single-photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes (PSs). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease [PD], multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]). DaTscan is an adjunct to other diagnostic evaluations.

DaTscan was not designed to distinguish among PD, MSA, and PSP. The effectiveness of DaTscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established.

IMPORTANT SAFETY INFORMATION ABOUT DATSCAN

CONTRAINDICATIONS

- DaTscan is contraindicated in patients with known hypersensitivity to the active substance, any of the excipients, or iodine

WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions:** Hypersensitivity reactions, generally consisting of skin erythema and pruritus, have been reported following DaTscan administration
- **Thyroid Accumulation:** The DaTscan injection may contain up to 6% of free iodide (iodine 123 or I-123). To decrease thyroid accumulation of I-123, block the thyroid gland at least one hour before administration of DaTscan; failure to do so may increase the long-term risk for thyroid neoplasia

ADVERSE REACTIONS

- In clinical trials, headache, nausea, vertigo, dry mouth, or dizziness of mild to moderate severity were reported. In postmarketing experience, hypersensitivity reactions and injection-site pain have been reported

DRUG INTERACTIONS

- Drugs that bind to the dopamine transporter with high affinity may interfere with the DaTscan image. The impact of dopamine agonists and antagonists on DaTscan imaging results has not been established

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Radioactive iodine products cross the placenta and can permanently impair fetal thyroid function. Administration of a thyroid blocking agent is recommended before the use of DaTscan in a pregnant woman. All radiopharmaceuticals have potential to cause fetal harm. There are no available data on DaTscan use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Advise pregnant woman of the potential risks of fetal exposure to radiation with the administration of DaTscan
- **Lactation:** Iodine 123 (I 123), the radionuclide in DaTscan, is present in human milk. There is no information on the effects on breastfed infants or on milk. Advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for at least 6 days after DaTscan administration to minimize radiation exposure to a breastfeeding infant
- **Pediatric Use:** The safety and efficacy of DaTscan have not been established in pediatric patients
- **Geriatric Use:** There were no differences in responses between elderly patients and younger patients that would require a dose adjustment
- **Renal and Hepatic Impairment:** The effect of renal or hepatic impairment on DaTscan imaging has not been established. The kidney excretes DaTscan; patients with severe renal impairment may have increased radiation exposure and altered DaTscan images

OVERDOSAGE

- It is unknown whether or not ioflupane is dialyzable. The major risks of overdosage relate to increased radiation exposure and long-term risk for neoplasia. In case of radioactivity overdosage, frequent urination and defecation should be encouraged to minimize radiation exposure to the patient

PROCEDURE — Radiation Safety

- DaTscan emits radiation and must be handled with safety measures to minimize radiation exposure to clinical personnel and patients

Prior to DaTscan administration, please read the enclosed full Prescribing Information for additional Important Safety Information.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 800 654 0118 (option 2, then option 1) or the FDA at 800 FDA 1088 or www.fda.gov/medwatch.



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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DaTscan safely and effectively. See full prescribing information for DaTscan.

DaTscan (Ioflupane I 123 Injection) for Intravenous Use
Initial U.S. Approval: 2011

-----INDICATIONS AND USAGE-----

DaTscan (Ioflupane I 123 Injection) is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations. (1)

-----DOSAGE AND ADMINISTRATION-----

- DaTscan emits gamma radiation and must be handled with safety measures. (2.1)
- Measure patient dose by a suitable radioactivity calibration system immediately prior to administration. (2.1)
- Administer a thyroid-blocking agent at least one hour before the dose of DaTscan. (2.2)
- The recommended DaTscan dose is 111 to 185 MBq (3 to 5 mCi). (2.4)
- Begin SPECT imaging between 3 and 6 hours post-injection. (2.6)

-----DOSAGE FORMS AND STRENGTHS-----

2.5 mL of sterile solution for intravenous injection in a single-use vial [74 MBq (2 mCi)/mL at calibration time]. (3)

-----CONTRAINDICATIONS-----

Known hypersensitivity to the active substance or to any of the excipients, or to iodine. (4)

-----WARNINGS AND PRECAUTIONS-----

- Hypersensitivity reactions have been reported following DaTscan administration. Have anaphylactic and hypersensitivity treatment measures available prior to DaTscan administration. (5.1)
- Administer a thyroid-blocking agent before DaTscan administration. (5.2)

-----ADVERSE REACTIONS-----

Hypersensitivity and injection site reactions have been reported following DaTscan administration. (6.2) In clinical trials, the most common adverse reactions, headache, nausea, vertigo, dry mouth or dizziness occurred in < 1% of subjects. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

Amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, selegiline, sertraline, citalopram and paroxetine may interfere with DaTscan imaging. (7) The effects of dopamine agonists and antagonists on DaTscan imaging have not been established.

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise a lactating woman to interrupt breastfeeding and pump and discard breastmilk for at least 6 days after DaTscan administration. (8.2)
- Pediatric: Safety and effectiveness have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2020

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- 2.2 Thyroid Blockade Before DaTscan Injection
- 2.3 Preparation and Administration
- 2.4 Recommended Dose
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety

DaTscan emits radiation and must be handled with safety measures to minimize radiation exposure to clinical personnel and patients. Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experienced in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. DaTscan dosing is based upon the radioactivity determined using a suitably calibrated instrument immediately prior to administration.

To minimize radiation dose to the bladder, encourage hydration prior to and following DaTscan administration in order to permit frequent voiding. Encourage the patient to void frequently for the first 48 hours following DaTscan administration [see *Dosage and Administration* (2.5)].

2.2 Thyroid Blockade Before DaTscan Injection

Before administration of DaTscan, administer Potassium Iodide Oral Solution or Lugol's Solution (equivalent to 100 mg iodide) or potassium perchlorate (400 mg) to block uptake of iodine 123 by the patient's thyroid. Administer the blocking agent at least one hour before the dose of DaTscan [see *Warnings and Precautions* (5.2)].

2.3 Preparation and Administration

- Assess pregnancy status before administering DaTscan to a female of reproductive potential.
- Use aseptic procedures and radiation shielding during preparation and administration. Inspect the DaTscan vial prior to administration and do not use it if the vial contains particulate matter or discoloration [see *Description* (11)]. Administer DaTscan as a slow intravenous injection (administered over a period of not less than 15 to 20 seconds) via an arm vein.

2.4 Recommended Dose

The recommended dose is 111 to 185 MBq (3 to 5 mCi) administered intravenously [see *Clinical Studies* (14)].

2.5 Radiation Dosimetry

The estimated radiation absorbed doses to an average adult from intravenous injection of DaTscan are shown in Table 1. 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).

Table 1 Estimated Radiation Absorbed Doses from DaTscan

ORGAN / TISSUE		ABSORBED DOSE PER UNIT ADMINISTERED ACTIVITY (μGy / MBq)
Adrenals		12.9
Brain		17.8
Striata		230
Breasts		7.8
Esophagus		10
Gallbladder Wall		26.4
GI Tract	Stomach Wall	11.2
	Small Intestine Wall	21.2
	Colon Wall ^a	39.8
	Upper Large Intestine Wall	38.1
	Lower Large Intestine Wall	42
Heart Wall		12.9
Kidneys		10.9
Liver		27.9
Lungs		41.2
Muscle		9.4
Esophagus		10
Osteogenic Cells		28.2
Ovaries		16.8
Pancreas		13
Red Marrow		9.2
Skin		6
Spleen		10.4
Testes		8.5
Thymus		10
Thyroid		9
Urinary Bladder Wall		53.1
Uterus		16.1
Total Body		11.3
EFFECTIVE DOSE PER UNIT ADMINISTERED ACTIVITY (μSv/MBq)		21.3

^a The absorbed dose to the colon wall is the mass-weighted sum of the absorbed doses to the upper and lower large intestine walls, $D_{\text{colon}} = 0.57D_{\text{ULI}} + 0.43D_{\text{LLI}}$ [Publication 80 of the ICRP (International Commission on Radiological Protection); Annals of the ICRP 28 (3), Oxford: Pergamon Press; 1998]

The Effective Dose resulting from a DaTscan administration with an administered activity of 185 MBq (5 mCi) is 3.94 mSv in an adult.

2.6 Imaging Guidelines

Begin SPECT imaging 3 to 6 hours following DaTscan administration. Acquire images using a gamma camera fitted with high-resolution collimators and set to a photopeak of 159 keV with a $\pm 10\%$ energy window. Angular sampling should be not less than 120 views over 360 degrees. Position the subject supine with the head on an off-the-table headrest, a flexible head restraint such as a strip of tape across the chin or forehead may be used to help avoid movement, and set a circular orbit for the detector heads with the radius as small as possible (typically 11 to 15 cm).

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 to 4.5 mm. Collect a minimum of 1.5 million counts for optimal images.

2.7 Image Interpretation

DaTscan images are interpreted visually, based upon the appearance of the striata. Reconstructed pixel size should be between 3.5 and 4.5 mm with slices 1 pixel thick. Optimum presentation of the reconstructed images for visual interpretation is transaxial slices parallel to the anterior commissure-posterior commissure (AC-PC) line. Determination of whether an image is normal or abnormal is made by assessing the extent (as indicated by shape) and intensity of the striatal signal. Image interpretation does not involve integration of the striatal image appearance with clinical signs and/or symptoms.

Normal:

In transaxial images, normal images are characterized by two symmetric comma- or crescent-shaped focal regions of activity mirrored about the median plane. Striatal activity is distinct, relative to surrounding brain tissue (Figure 1).

Abnormal:

Abnormal DaTscan images fall into at least one of the following three categories (all are considered abnormal).

- Activity is asymmetric, e.g. activity in the region of the putamen of one hemisphere is absent or greatly reduced with respect to the other. Activity is still visible in the caudate nuclei of both hemispheres resulting in a comma or crescent shape in one and a circular or oval focus in the other. There may be reduced activity between at least one striatum and surrounding tissues (Figure 2).
- Activity is absent in the putamen of both hemispheres and confined to the caudate nuclei. Activity is relatively symmetric and forms two roughly circular or oval foci. Activity of one or both is generally reduced (Figure 3).
- Activity is absent in the putamen of both hemispheres and greatly reduced in one or both caudate nuclei. Activity of the striata with respect to the background is reduced (Figure 4).

Figure 1

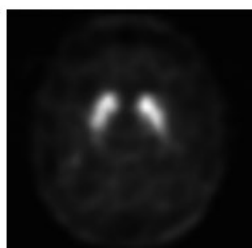


Figure 2

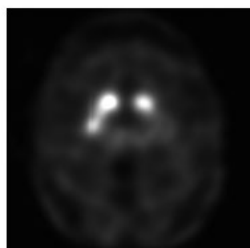


Figure 3

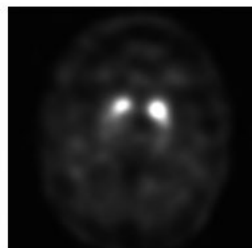
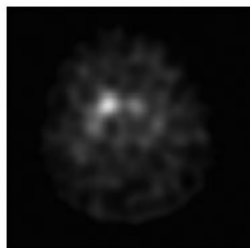


Figure 4



3 DOSAGE FORMS AND STRENGTHS

Single-use vials containing 185 MBq (5 mCi) in 2.5 mL sterile solution for intravenous injection [74 MBq (2 mCi) per mL at calibration time].

4 CONTRAINDICATIONS

DaTscan is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients, or to iodine.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported following DaTscan administration [see Adverse Reactions (6.2)]. The reactions have generally consisted of skin erythema and pruritis and have either resolved spontaneously or following the administration of corticosteroids and anti-histamines. Prior to administration, question the patient for a history of prior reactions to DaTscan. If the patient is known or strongly suspected of having had a hypersensitivity reaction to DaTscan, the decision to administer DaTscan should be based upon an assessment of the expected benefits compared to the potential hypersensitivity risks. Have anaphylactic and hypersensitivity treatment measures available prior to DaTscan administration and, following administration, observe patients for symptoms or signs of a hypersensitivity reaction.

5.2 Thyroid Accumulation

The DaTscan injection may contain up to 6% of free iodide (iodine 123). To decrease thyroid accumulation of iodine 123, block the thyroid gland before administration of DaTscan [see Dosage and Administration (2.2)]. Avoid the use of Potassium Iodide Oral Solution or Lugol's Solution in patients who are sensitive to such products. Failure to block thyroid uptake of iodine 123 may result in an increased long term risk for thyroid neoplasia.

6 ADVERSE REACTIONS

6.1 Clinical Study Experience

The data from clinical studies reflect exposure to DaTscan in 942 subjects with a mean age of 66 years (range 25 to 90 years). Among these subjects, 42% were women and 99% Caucasian. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of DaTscan cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In clinical trials, no serious adverse reactions were reported. Other adverse reactions occurred at a rate of 1% or less and the reported events consisted of headache, nausea, vertigo, dry mouth or dizziness. These reactions were of mild to moderate severity.

6.2 Postmarketing Experience

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the postmarketing experience, hypersensitivity reactions have been reported. The reactions generally related to rash and pruritis within minutes of DaTscan administration. The reactions either resolved spontaneously or following the administration of corticosteroids and antihistamines. Injection site pain has also been reported.

7 DRUG INTERACTIONS

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 minimize the interference with a DaTscan image is unknown.

The impact of dopamine agonists and antagonists upon DaTscan imaging results has not been established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Radioactive iodine products cross the placenta and can permanently impair fetal thyroid function. Administration of an appropriate thyroid blocking agent is recommended before use of DaTscan in a pregnant woman to protect the woman and fetus from accumulation of I 123 [see Dosage and Administration (2.2)].

There are no available data on DaTscan use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with ioflupane I 123. All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. Administration of DaTscan at a dose of 185 MBq (5 mCi) results in an absorbed radiation dose to the uterus of 0.3 rad (3.0 mGy). Radiation doses greater than 15 rad (150 mGy) have been associated with congenital anomalies but doses under 5 rad (50 mGy) generally have not. Advise pregnant women of the potential risks of fetal exposure to radiation doses with administration of DaTscan.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Iodide 123 (I 123), the radionuclide in DaTscan, is present in human milk. There is no information on the effects on the breastfed infant or on milk production. Advise a lactating woman to interrupt breastfeeding and pump and discard breastmilk for at least 6 days (>10 physical half-lives) after DaTscan administration in order to minimize radiation exposure to a breastfed infant.

8.4 Pediatric Use

DaTscan is not indicated for use in children. The safety and efficacy of DaTscan have not been established in pediatric patients.

8.5 Geriatric Use

In the two principal clinical studies, 45% of the subjects were aged 65 and over. There were no differences in response compared to younger subjects that would require a dose adjustment. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Renal and Hepatic Impairment

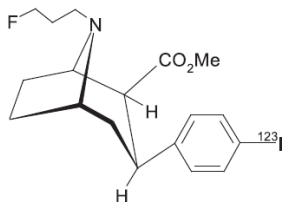
The effect of renal or hepatic impairment upon DaTscan imaging has not been established. DaTscan is excreted by the kidney and patients with severe renal impairment may have increased radiation exposure and altered DaTscan images.

10 OVERDOSAGE

The clinical consequence of overdose with DaTscan has not been reported. It is unknown whether or not ioflupane is dialyzable. Due to the small quantity of ioflupane in each vial, overdosage with ioflupane is not expected to result in pharmacologic effects. The major risks of overdose relates predominantly to increased radiation exposure, with the long-term risks for neoplasia. In case of overdosage of radioactivity, frequent urination and defecation should be encouraged to minimize radiation exposure to the patient; care should be taken to avoid contamination from the radioactivity eliminated by the patient.

11 DESCRIPTION

DaTscan [Ioflupane I 123 Injection] is a sterile, pyrogen-free radiopharmaceutical for intravenous injection. The clear and colorless solution is supplied in single-use vials in which each milliliter contains 0.07 to 0.13 µg ioflupane, 74 MBq (2 mCi) of iodine 123 (as ioflupane I 123) at calibration time, 5.7 mg acetic acid, 7.8 mg sodium acetate and 0.05 mL (5%) ethanol. The pH of the solution is between 4.2 and 5.2. Ioflupane I 123 has the following structural formula:



11.1 Physical Characteristics

Iodine 123 is a cyclotron-produced radionuclide that decays to ^{123}Te by electron capture and has a physical half-life of 13.2 hours. The photon that is useful for detection and imaging studies is listed in Table 2.

Table 2

Principal Radiation Emission Data – Iodine-123

Radiation	Energy Level (keV)	Abundance (%)
Gamma	159	83

11.2 External Radiation

The specific gamma-ray constant for iodine 123 is 1.6 R/mCi-hr at 1 cm. The first half-value thickness of lead (Pb) for iodine 123 is 0.04 cm. The relative transmission of radiation emitted by the radionuclide that results from interposition of various thicknesses of Pb is shown in Table 3 (e.g., the use of 2.16 cm Pb will decrease the external radiation exposure by a factor of about 1,000).

Table 3

Reduction in In-air Collision Kerma Caused by Lead Shielding ^a

Shield Thickness cm of lead (Pb)	Reduction in In-air Collision Kerma
0.04	0.5
0.13	10^{-1}
0.77	10^{-2}
2.16	10^{-3}
3.67	10^{-4}

^a Calculation based on attenuation and energy-transfer coefficients obtained from National Institute of Standards & Technology Internal Report NISTIR 5632.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active drug substance in DaTscan is N- ω -fluoropropyl-2 β -carbomethoxy-3 β -(4-[^{123}I]iodophenyl)nortropane or ioflupane I 123.

In vitro, ioflupane binds reversibly to the human recombinant dopamine transporter (DaT) ($K_i = 0.62$ nM; $\text{IC}_{50} = 0.71$ nM). Autoradiography of post-mortem human brain slices exposed to radiolabeled ioflupane shows concentration of the radiolabel in striatum (caudate nucleus and putamen). The specificity of the binding of ioflupane I 125 to dopamine transporter was demonstrated by competition studies with the DaT inhibitor GBR 12909 (a dopamine reuptake inhibitor), the serotonin reuptake inhibitor citalopram, and the norepinephrine reuptake inhibitor desipramine in post-mortem human brain slices exposed to radiolabeled ioflupane. Citalopram reduced binding in the neocortex and thalamus with only minor effects in the striatum. This indicated that the binding in the cortex and thalamus is mainly to the serotonin reuptake sites. Desipramine showed no effect on the level of striatal binding of ioflupane I 125, but reduced extrastriatal binding by 60 to 85%. The binding of ioflupane I 125 to the striatum was abolished in the presence of high concentrations of GBR 12909, indicating selectivity of ioflupane binding for the pre-synaptic DaT.

Following administration of DaTscan to humans, radioactive decay of the iodine 123 emits gamma radiation which can be detected externally using gamma detectors, allowing visualization of the brain striata through SPECT imaging [see *Clinical Pharmacology* (12.3)].

12.2 Pharmacodynamics

As DaTscan contains a very small quantity of ioflupane, no ioflupane pharmacologic effects are expected [see *Description* (11)].

12.3 Pharmacokinetics

The pharmacokinetics of ioflupane I 123 were studied by monitoring radioactivity following intravenous injection; only 5% of the administered radioactivity remained in whole blood at 5 minutes post-injection. Uptake in the brain reached approximately 7% of injected radioactivity at 10 minutes post-injection and decreased to 3% after 5 hours; striata to background ratios were relatively constant between 3 and 6 hours post-injection. About 30% of the whole brain radioactivity was attributed to striatal uptake. By 48 hours post-injection, approximately 60% of the injected radioactivity has been excreted in the urine, with fecal excretion estimated to be approximately 14%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies on reproductive toxicity have not been conducted. Ioflupane showed no evidence of mutagenic potential in *in vitro* or *in vivo* mutagenicity studies. Studies to assess the carcinogenic potential of ioflupane have not been performed.

13.2 Animal Toxicology and/or Pharmacology

Single- and repeated-dose intravenous toxicity studies have been performed using ioflupane in rats, rabbits, and dogs. Additionally, single-dose acute toxicity studies have been performed in cynomolgus monkeys. No mortality or other toxicity was observed at doses up to 5,500 times the maximum clinical dose of DaTscan; at doses greater than 1,500 times the maximum clinical dose, pharmacological responses such as mydriasis and hyperactivity were seen in some species.

14 CLINICAL STUDIES

The safety and efficacy of DaTscan were evaluated in two multicenter, 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 99 patients in Study 1, 44% were female, 42% were aged 65 or over and all were Caucasian; among the 185 patients in Study 2, 35% were female, 48% were aged 65 or over and 99% 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 4 shows the positive percent agreement and negative percent agreement of the DaTscan image results with the reference clinical diagnostic standard. Positive percent agreement represents the percent of patients with abnormal DaTscan images among all the patients with a clinical diagnostic reference standard of PS. The negative percent agreement represents the percent of patients with normal DaTscan images among the patients with a non-PS clinical diagnostic reference standard.

Table 4: Positive and Negative Percent Agreements for Studies 1 and 2

	Positive percent agreement (95 % CI) (% patients with an abnormal DaTscan image among patients with PS)	Negative percent agreement (95 % CI) (% patients with a normal DaTscan image among patients with non-PS)
Study 1 (patients with early signs and/or symptoms of PS)		
Reader A, n = 99	77 (66, 87)	96 (82, 100)
Reader B, n = 96	78 (66, 87)	96 (82, 100)
Reader C, n = 98	79 (67, 87)	96 (82, 100)
Study 2 (patients with established diagnoses of PS or ET)		
Reader A, n = 185	93 (88, 97)	96 (81, 100)
Reader B, n = 185	97 (93, 99)	74 (54, 89)
Reader C, n = 185	96 (92, 99)	85 (66, 96)
Reader D, n = 185	92 (87, 96)	93 (76, 99)
Reader E, n = 185	94 (90, 97)	93 (76, 99)

The effectiveness of DaTscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

DaTscan is supplied in 10-mL glass vials containing a total volume of 2.5 mL of solution with a total radioactivity of 185 MBq (5 mCi) at calibration time. Each vial is enclosed in a lead container of appropriate thickness.

NDC 17156-210-01

Storage

Store DaTscan at 20° to 25°C (68° to 77°F). This product does not contain a preservative. Store DaTscan within the original lead container or equivalent radiation shielding.

Do not use DaTscan (Ioflupane I 123 Injection) preparations after the expiration date and time stated on the label.

Handling

This preparation is approved for use by persons licensed by the Illinois Emergency Management Agency pursuant to 32 IL. Adm. Code Section 330.260(a) and 335.4010 or equivalent licenses of the Nuclear Regulatory Commission or an Agreement State.

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform their physician or healthcare provider if they:

1. are pregnant. Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with DaTscan [see Use in Specific Populations (8.1)].
2. are breast feeding. Advise a lactating woman to interrupt breastfeeding and pump and discard breastmilk for at least 6 days (>10 physical half-lives) after DaTscan administration in order to minimize radiation exposure to a breastfed infant [see Use in Specific Populations (8.2)].
3. are sensitive to DaTscan.
4. are sensitive to Potassium Iodide Oral Solution, or Lugol's Solution.
5. have reduced renal or hepatic function.

Instruct patients to increase their level of hydration prior to and after receiving DaTscan and to void frequently for the first 48 hours following DaTscan administration.



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