DaTscan (Ioflupane I 123 Injection) for Parkinsonian Syndrome

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.

Dosage And Administration

1. DaTscan emits gamma radiation and must be handled with safety measures

2. Administer a thyroid blocking agent at least one hour before the dose of DaTscan The recommended DaTscan dose is 111 to 185 MBq (3 to 5 mCi).

3. Measure patient dose by a suitable radioactivity calibration system immediately prior to administration

4. Begin SPECT imaging between 3 and 6 hours post injection.

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].

Contraindications

Known hypersensitivity to the active substance or to any of the excipients, or to iodine

Warnings And Precautions

1. Hypersensitivity reactions have been reported following DaTscan administration. Have anaphylactic and hypersensitivity treatment measures available prior to DaTscan administration.

2. Administer a thyroid-blocking agent before DaTscan administration.

Adverse Reactions

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

Drug Interactions

1. Amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, selegiline, sertraline, citalopram and paroxetine may interfere with DaTscan imaging.

2. The effects of dopamine agonists and antagonists on DaTscan imaging have not been established.

Use In Specific Populations

Pregnancy: No human or animal data. Any radiopharmaceutical, including DaTscan, may cause fetal harm. Use only if clearly needed.

Nursing Mothers: A decision should be made whether to interrupt nursing after DaTscan administration or not to administer DaTscan, taking into consideration the importance of the drug to the mother. Based on the physical half-life of iodine 123 (13.2 hours), nursing women may consider interrupting nursing and pumping and discarding breast milk for 6 days after DaTscan administration in order to minimize risks to a nursing infant.

Pediatric: Safety and effectiveness have not been established.

Radiation Safety

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

2. 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.

3. DaTscan dosing is based upon the radioactivity determined using a suitably calibrated instrument immediately prior to administration.

4. 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

5. 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

6. 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

7. Administer DaTscan as a slow intravenous injection (administered over a period of not less than 15 to 20 seconds) via an arm vein.

8. The recommended dose is 111 to 185 MBq (3 to 5 mCi) administered intravenously

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).

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
GI Tract	Small Intestine Wall	21.2
GI Tract	Colon Wall [a]	39.8
GI Tract	Upper Large Intestine Wall	38.1
GI Tract	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, $D_{colon} = 0.57D_{ULI} + 0.43D_{LLI}$ [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.

Imaging Guidelines

1. Begin SPECT imaging 3 to 6 hours following DaTscan administration.

2. Acquire images using a gamma camera fitted with high-resolution collimators and set to a photopeak of 159 keV with a ± 10% energy window. Angular sampling should be not less than 120 views over 360 degrees.

3. 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).

4. 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.

5. Collect a minimum of 1.5 million counts for optimal images.

Image Interpretation

1. 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.

2. Optimum presentation of the reconstructed images for visual interpretation is transaxial slices parallel to the anterior commissure-posterior commissure (ACPC) 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.

3. 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

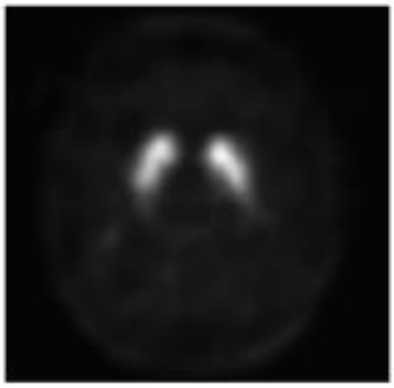
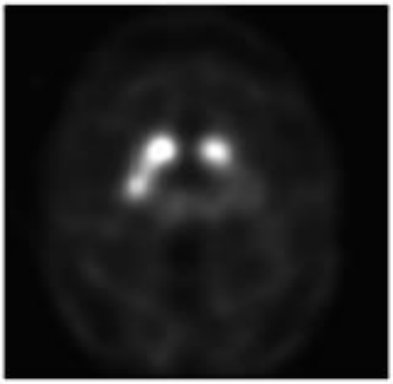


Figure 2



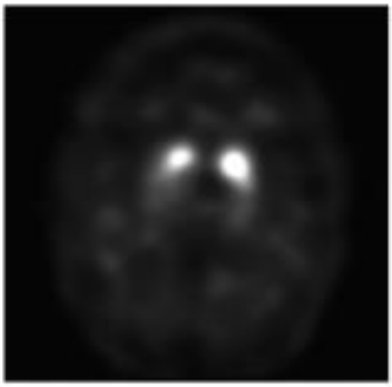


Figure 3

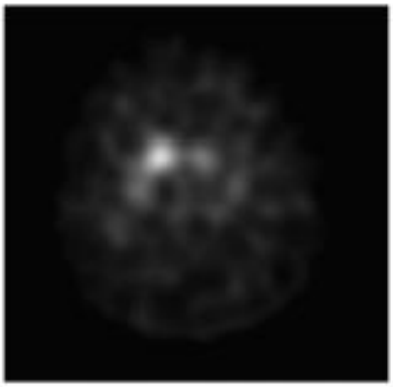


Figure 4

Dosage Forms and Strengths

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

Contraindications

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

Warnings And Precautions

Hypersensitivity Reactions

1. Hypersensitivity reactions have been reported following DaTscan administration. The reactions have generally consisted of skin erythema and pruritis and have either resolved spontaneously or following the administration of corticosteroids and anti-histamines.

2. 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.

3. Have anaphylactic and hypersensitivity treatment measures available prior to DaTscan administration and, following administration, observe patients for symptoms or signs of a hypersensitivity reaction.

Thyroid Accumulation

1. 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.

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

Clinical Study Experience

1. The data from clinical studies reflect exposure to DaTscan in 942 subjects with a mean age of 66 years (range 25 to 90 years).

2. Among these subjects, 42% were women and 99% Caucasian.

3. 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.

4. 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**

1. 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.

2. 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.

Pediatric Use

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

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.

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.

Overdosage

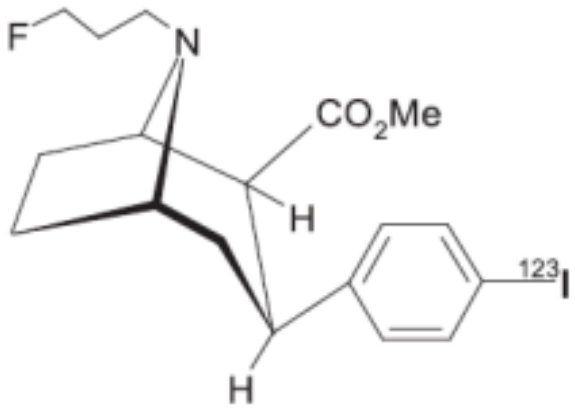
1. The clinical consequence of overdose with DaTscan has not been reported. It is unknown whether or not ioflupane is dialyzable. Due to the small quantity of ioflupane in each vial, overdosage with ioflupane is not expected to result in pharmacologic effects.

2. The major risks of overdose relate predominantly to increased radiation exposure, with the long-term risks for neoplasia.

3. 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.
4.

Chemical characteristics

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:



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

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). T

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}

Clinical Pharmacology

Mechanism of Action

1. In vitro, ioflupane binds reversibly to the human recombinant dopamine transporter (DaT). Autoradiography of post-mortem human brain slices exposed to radiolabeled ioflupane shows concentration of the radiolabel in striatum (caudate nucleus and putamen).

2. 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.

3. As DaTscan contains a very small quantity of ioflupane, no ioflupane pharmacologic effects are expected

Pharmacokinetics

1. following intravenous injection; only 5% of the administered radioactivity remained in whole blood at 5 minutes post injection.
2. The effectiveness of DaTscan as a screening or confirmatory test and for monitoring has not been established.

3. By 48 hours post injection, approximately 60% of DaTscan has been excreted in the urine, with fecal excretion estimated to be approximately 14%.

Carcinogenesis, Mutagenesis, Impairment of Fertility Storage

1. Studies on reproductive toxicity have not been conducted

2. Studies to assess the carcinogenic potential of ioflupane have not been performed. shielding.

Clinical Studies

1. 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.

2. In 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 administration.

3. 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 system. 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)].

4. 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)