

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022454Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

### Cross-Discipline Team Leader Review

<b>Date</b>	January 3, 2010
<b>From</b>	Louis Marzella MD PhD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 022454
<b>Applicant</b>	GE Healthcare
<b>Date of Submission</b>	November 16, 2010
<b>PDUFA Goal Date</b>	January 14, 2011
<b>Proprietary Name / Established (USAN) names</b>	DaTscan loflupane I 123 injection
<b>Dosage forms / Strength</b>	Sterile injection/ for intravenous administration 2mCi/ml at calibration time 0.33mcg iopflupane/vial
<b>Proposed Indication</b>	DaTscan (loflupane 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
<b>Recommended:</b>	Approval

#### Recommended Regulatory Action

The present November 16, 2010 submission is a class 1 response to FDA's December 23, 2009 complete response letter.

The CDTL reviewer agrees with the recommendation by the FDA's Clinical (Phillip Davis MD), Chemistry Manufacturing and Controls (CMC, Ravindra Kasliwal PhD), and Clinical Pharmacology (Christy John PhD) reviewers that the application be approved and that the postmarketing commitment to study the effect of dopaminergic drugs on DaTscan images be released.

A response by the Applicant to an FDA request for minor labeling changes was pending at the time the CDTL review was filed.

## **Overview**

### Original submission

On March 6, 2009 the Applicant filed the original NDA for a new molecular entity (loflupane I 123) a radioiodinated tropane analogue supplied as a sterile solution formulated for intravenous administration. The drug product (DaTscan) is a diagnostic radiopharmaceutical proposed for use as a diagnostic agent.

At an August 11, 2009 meeting the FDA 's Peripheral and Central Nervous System Advisory Committee supplemented with medical imaging experts discussed the NDA and recommended that DaTscan be approved.

Within the NDA review team, the CMC, Toxicology and Pharmacology reviewers recommend an approval action. On the other hand, the Statistical reviewer (Mark Levenson PhD) did not find the efficacy data to be sufficiently persuasive to recommend approval. The CDTL and the primary clinical reviewers determined that the totality of the preclinical and clinical data show that DaTscan allows visualization of the dopamine transporter within the striatum in the brain and concluded that the available clinical data show a favorable risk benefit for the adjunctive use of DaTscan in patients presenting with symptoms and signs of Parkinsonian syndrome.

The CDTL recommended approval of the NDA pending agreement by the applicant to revise the product's package insert label as recommended by the NDA review team.

Agreement on labeling was not reached and FDA issued a complete response letter on September 8, 2009.

### First resubmission

On October 26, 2009 the applicant provided a complete response. The submission did not adequately address the FDA's requests that:

- the package insert and container labels reflect the current status of the drug as a narcotic substance under the Controlled Substances Act
- the applicant design postmarketing clinical studies to assess
  - the agreement between DaTscan imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients
  - the impact of dopaminergic drugs upon DaTscan image results.

As a result, FDA issued a complete response letter on December 23, 2009.

### Second resubmission

The present November 16, 2010 submission is a class 1 response to FDA's December 23, 2009 complete response letter. The submission adequately addresses the outstanding labeling and postmarketing clinical studies issues as follows.

### **Summary of Present Submission**

#### **1) Request for revised text to support approval of a controlled substance**

##### Background

The 12/11/2009 review by CSS requested the following:

- The drug's status as a controlled substance must be clearly marked on the outside of the product packaging. The CII symbol must appear after the commercial name.
- Under the HIGHLIGHTS OF PRESCRIBING INFORMATION, The second paragraph should read: DaTscan (loflupane I 123 Injection) for Intravenous Use, CII Initial U.S. Approval: 2009
- Section 9, DRUG ABUSE AND DEPENDENCE needs to be added. This section should contain the following language: "loflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act."

##### Revised labeling

The revised container (vial and shield) labeling shows the CII symbol as requested (see below).





The revised package insert contains the following new information

**DaTscan (Ioflupane I 123 Injection) for Intravenous Use, CII  
Initial U.S. Approval: 2010**

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**

**FULL PRESCRIBING INFORMATION**

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**

Ioflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act.



Assessment of revised label

*Container labeling.* The CMC reviewer found the labeling to be acceptable. The DMEPA reviewer requested that the NDC number be relocated to the top third of the principal display panel.

*Package insert.* The CSS reviewer requested the following changes to 9.1.

- Strike the statement:  (b) (4)
- Add the statement: "A DEA license is required for handling or administering this controlled substance."

**2) Request for postmarketing commitments**

The Applicant provides a complete clinical protocol (GE-001-011) to address the Post-Approval Commitment for a study of DaTscan imaging in non-Caucasians.

This protocol was submitted under IND 101,016 and the clinical reviewer (Dr, Davis) judged it to be satisfactory. In response to FDA's information request during the present review cycle the Applicant provided a satisfactory timeline for the completion and reporting of the study.

The applicant requests to be released from the Post-Approval Commitment to study the effects of dopaminergic drugs on DaTscan images. The justification of this request was submitted under IND 101,016. The FDA's Clinical Pharmacology reviewer (Dr. John), and the Neurology consultant (Dr. Kenneth Bergmann) determined that the existing data provide sufficient safety information and that the package insert adequately describes the limitations of current knowledge about the potential effect of CNS drugs on DaTscan images.

The CDTL agrees with the FDA reviewers that the protocol for the study of DaTscan in non-Caucasian is acceptable and that the justification for not conducting the drug interaction study is reasonable

### **3) Safety update**

The CDTL agrees with Dr. Davis that the applicant has not identified any new safety signals. Therefore, the reporting requirement for the resubmission has been satisfied.

### **4) Proprietary name review**

The 5/29/2009 and 12/14/2009 reviews by DMEPA and the 5/7/2009 review by DDMAC found the name to be acceptable. A final review by DMEPA is pending.

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## Cross Discipline Team Leader Review

<b>Date</b>	August 28, 2009
<b>From</b>	Louis Marzella M.D., Ph.D.
<b>Subject</b>	Cross-discipline Team Leader Review
<b>NDA/BLA #</b>	22-454
<b>Supplement#</b>	Original submission
<b>Applicant</b>	GE Healthcare
<b>Date of Submission</b>	March 19, 2009
<b>PDUFA Goal Date</b>	September 9, 2009
<b>Proprietary Name Established (USAN) names</b>	- DaTSCAN - Ioflupane I 123
<b>Dosage form Strength</b>	- Sterile Injection for Intravenous Administration - 2 mCi/ml (5 mCi/vial) at calibration time - 0.33 mcg/vial ioflupane
<b>Proposed Indication</b>	Detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography
<b>Recommended:</b>	Approval

### 1. Introduction

This New Drug Application (NDA 22454) is for a new molecular entity (Ioflupane I 123) a radioiodinated tropane analogue supplied as a sterile solution formulated with ethanol (b) (4) and acetate (b) (4) for intravenous administration. The drug product (Datscan) is a diagnostic radiopharmaceutical proposed for use as a diagnostic agent.

The proposed indication statement is: “for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.”

Clinical examination and brain histopathology at postmortem are the only diagnostic modalities available for patients with progressive irreversible dopaminergic neurodegeneration. Diagnostic tests are an unmet medical need for these serious disorders. For this reason the NDA was granted a priority review designation.

All the data provided in this NDA submission were collected in non-IND clinical trials conducted in Europe. The review team focused on the sponsor studies DP008-003, PDT3004, and PDT301 for confirmation and support of efficacy. In this review the studies will be designated 003, 004 and 301 respectively. Each study was a single-arm, multi-center study evaluating Datscan imaging relative to clinical diagnosis. Studies 003

and 004 enrolled patients with movement disorder; study 301 enrolled patients with dementia.

The CDTL reviewer reviewed the sponsor's NDA submission, the CMC, clinical and statistical reviews, and the DSI reports.

## **2. Background**

Certain neurologic disorders with abnormalities in movement and cognition share a common neuropathologic feature, namely, the progressive, irreversible loss of specific neurons located in the basal ganglia in the brain. The portion of the basal ganglia affected by these disorders is a nucleus containing pigmented neurons (substantia nigra) that synapse with another nucleus called the striatum. These neurons make up the nigrostriatal pathway. There are two striata in the brain and anatomically they are shaped like two commas. The commas can be further subdivided visually into "heads" containing the caudate nuclei, and "tails" containing the putamen nuclei.

The affected neurons in this nigrostriatal pathway are called dopaminergic because dopamine is the neurotransmitter used for signaling between the neurons. Dopaminergic neurons contain a cell surface protein (dopamine transporter, DaT) that stops neuronal signaling by binding dopamine in the synapse and transporting it back into the pre-synaptic neuron. The Datscan active ingredient Ioflupane I 123 binds to DaT, and the gamma rays released from the radioactive decay of the radionuclide can be imaged by a Single Photon Emission Computed Tomography (SPECT) camera to visualize the striatum.

Disorders of movement and cognition associated with loss of dopaminergic nigrostriatal neurons include Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB). Histopathology of postmortem specimens shows that the density of dopaminergic neurons in the nigrostriatum of affected patients is lower than the density in controls. Therefore DaT is a candidate for the assessment of the integrity of presynaptic dopaminergic nerve terminals in these patients.

Postmortem brain histopathology is considered the gold standard for diagnosis and no diagnostic tests are available currently other than clinical examination. Examination by a movement disorder specialist is considered the most acceptable reference standard particularly if baseline assessment is combined with a follow up assessments ideally for three years.

### Regulatory history of Datscan

In July 2000 Datscan was approved for marketing in the European Union with a diagnostic indication.

In January and August 2008 the sponsor met with FDA to discuss the existing clinical data for Datscan.

The sponsor proposed the submission of two studies in patients with movement disorders (#003 and 004) and two studies in patients with dementia with Lewy bodies (# 301 and the Walker study) as the principal confirmatory and supportive efficacy studies. FDA stated that the Sponsor’s clinical development program could not support a claim of detection of loss of functional nigrostriatal dopaminergic neurons. FDA also cited a number of shortcomings in the design of the studies that included reliability of the reference standard, relevance of study population to the population of intended use. FDA recommended that the Sponsor conduct an additional phase 3 study to evaluate the diagnostic performance of Datscan.

### 3. CMC

Datscan (Ioflupane I 123 Injection) is a diagnostic radiopharmaceutical for intravenous injection. It is supplied as a sterile, non-pyrogenic, aqueous solution containing 5 mCi Ioflupane I 123 at reference time and date. Each package contains one vial with 2.5 mL of solution containing 2.0 mCi/mL Ioflupane I 123 at the time of reference. No other manipulations to the drug product are needed prior to its administration. The recommended dosage is 3 to 5 mCi (maximum of 0.33 mcg ioflupane). The composition in the unit dose is summarized in **Table 1**.

<b>Table 1. Composition of Drug Product</b>		
<b>Ingredient</b>	<b>Amount</b>	<b>Function</b>
[ <sup>123</sup> I]Ioflupane	74 MBq/mL (2 mCi/mL) at reference time	Drug Substance
Ioflupane (b) (4)	(b) (4)	(b) (4)
Ethanol	0.05 mL/mL	(b) (4)
Sodium Acetate (b) (4)	(b) (4)	(b) (4)

The drug substance is manufactured (b) (4). The I-123 radioisotope is cyclotron-produced and has a physical half-life of 13.2 hours. (b) (4)

Because of the short half-life of 123I (13.2 h), the product does not contain anti-microbial preservatives (b) (4). Each vial is

placed in a lead-lined shipping container. The proposed product expiry is 7 hours after time of reference [REDACTED] (b) (4) After this time, the radioactivity has decayed to below the recommended dosage.

#### Microbiology review

The FDA microbiology reviewer Dr. Riely found the submission acceptable

#### CMC review

The FDA CMC reviewer Dr. Kasliwal found the submission to be acceptable

#### Facilities inspection

The manufacturing facilities were inspected by the Offices of Compliance and New Drug Quality Assessment and were found to be acceptable.

The CMC reviewers recommend an approval action with no post-marketing commitments or risk modification steps.

### **4. Nonclinical Pharmacology/Toxicology**

Single dose and repeat-dose toxicity studies were conducted in rats, rabbits and cynomolgus monkeys. No treatment-related mortality was reported in any of these studies. The no observed adverse effect levels in various studies were typically 100X or greater than the maximum human dose. Cardiovascular, respiratory and behavioral safety studies showed no safety signals.

The standard ICH battery of tests, including two *in vitro* assays covering the endpoints of gene mutation (in bacteria) and chromosomal effects (in cultured human lymphocytes and in mouse bone marrow), were evaluated. The tests were negative, indicating that ioflupane demonstrates no genotoxicity potential.

Intravenous injection of ioflupane in rats and non-human primates followed by imaging showed localization of the molecule to the striatum. Retention in the striatum ranged from 2 to 5 fold higher than retention in regions with “non-specific” uptake (e.g. cerebral cortex and cerebellum)

In a mouse model of toxin-induced dopaminergic neuronal dysfunction, administration of ioflupane followed by SPECT imaging showed correlation between the SPECT findings and the extent of toxin damage to dopaminergic neurons (quantitated by *ex vivo* DaT immunoreactivity)

The FDA toxicologist Dr. Awe recommended approval of the NDA.

## **5. Clinical Pharmacology/Biopharmaceutics**

### Biodistribution

Ioflupane I 123 activity in the blood is 5% of the administered activity at 5 minutes post-injection. Activity in the brain is 7% of administered activity at 10 minutes post-injection and 3% at 5 hours. SPECT imaging should begin 3 to 6 hours post-injection. Striatal activity accounts for 30% of the whole brain activity. At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine, and 14% is excreted in the urine. The estimated level of dopamine transporter occupancy in the human striatum following administration of Datscan (5 mCi) is 1% as shown in phase 2 clinical studies and does not cause pharmacological effect in humans.

### Pharmacodynamics

Autoradiography of slices of human brain exposed to ioflupane showed selective binding to the striata with blockade of this binding by DaT-avid competitors.

The affinity of DaTSCAN for human and animal dopamine transporter (DaT) has been evaluated in competitive binding studies at test agent doses between 0.1 nM and 100 uM. The affinity of ioflupane for the rodent dopamine transporter and its selectivity to other receptor and transmitter uptake target was studied. The binding of [3H]WIN35,428 (specific ligand for dopamine transporter) was inhibited with  $K_i$  of 3.3 nM and an  $IC_{50}$  of 3.7 nM. Ioflupane also inhibited binding at the human recombinant dopamine transporter with a  $K_i$  of 0.62 nM and an  $IC_{50}$  of 0.70 nM.

### Drug interactions

Formal drug-drug interactions studies in humans have not been performed. Based on Datscan's mechanism of action, drug interactions are possible and might result in false positive or false negative imaging results. Drugs affecting dopaminergic neurotransmission might influence binding of ioflupane I 123 to DaT either directly by competitive binding or indirectly by influencing the expression of the transporter on the cell surface. If such interactions exist the washout time needed to avoid interference with imaging would need to be evaluated. Particularly important is the potential effect of dopaminergic drugs on DaT expression. Published studies have found no consistent effects in animal or human studies. However most studies have important limitations and no cross-over studies with adequate power to detect important differences have been performed.

The following drugs which may interfere with Datscan binding include: benztropine (an anti-cholinergic tropane); cocaine (a tropane); mazindol, amphetamine, phentermine and methylphenidate (sympathomimetics); bupropion (an atypical anti-depressant used to treat nicotine addiction); and sertraline (and possibly other serotonin re-uptake inhibitors).

The CDTL reviewer agrees with the recommendation by the clinical reviewer to request further study of the influence of dopaminergic drugs on Datscan imaging.

## 6. Clinical/Statistical- Efficacy

### Scientific data integrity

The Sponsor reported that there were no major systemic deviations from the study protocols in the conduct of the studies and in the image review process.

The quality of the data was verified by FDA through inspection of two clinical study centers and of the central imaging laboratory. No major deficiencies that could compromise the integrity of the data were identified.

### **Overview of the Principal Efficacy Study Protocols**

Each of the three trials was single arm, multicenter; the study population consisted of patients with and without a Parkinsonian syndrome or dementia as determined from the clinical diagnosis. The principal efficacy outcome was the blinded independent assessment of the SPECT images with comparison of the image assessments to the clinical diagnoses. Among the three studies, only study 301 had pre-specified statistical tests. In particular, the sensitivity and specificity were to be tested against the thresholds of 0.65 and 0.73 respectively. The primary statistical analysis for studies 003 and 0004 were confidence intervals. For these studies, there were no pre-specified statistical tests or thresholds for the confidence intervals.

**Table 2. Study Protocols**

	<b>DP008-003</b>	<b>PDT3004</b>	<b>PDT301</b>
Study Population	Movement disorder: diagnoses PD, MSA, PSP, ET; HV	Movement disorder: early signs of PS (PD, ET, other); HV	Dementia: probable DLB, possible DLB, AD, VaD
Primary Outcome	PS vs. non-PS (excluding HV)	Probable PD, Possible PD vs. ET, other (including HV)	Probable-DLB vs. non-DLB
Non-reference standard	Local, based on referral and baseline diagnosis at baseline	Central, based on video evaluations up to 36months	Central, based on baseline evaluation
Image Evaluations	Local un-blinded and 5 central independent blinded readers	Local and 3 central, independent, blinded readers	3 central, independent, blinded

For each of the trials the following descriptive image evaluation criteria were used.

#### *Normal.*

Uptake of the tracer present in both right and left putamen and caudate nuclei. Image largely symmetrical with approximately equal levels of uptake on both left and right

sides. Activity contained close to the center of the image forming two crescent shaped areas of uptake.

*Abnormal*

*Type 1.* Asymmetric uptake with normal or almost normal putamen activity in one hemisphere and a more marked change on the other side.

*Type 2.* Uptake reduced in the putamen on both the right and left sides. Activity confined to the caudate nuclei and forms two roughly symmetrical, circular areas.

*Type 3.* Uptake virtually absent from both putamen and caudate nuclei on each side of the brain resulting in a reduction in contrast and the visualization of background activity throughout the rest of the image.

**Results**

Demographics

The mean overall age was 66.4 years ranging from 25 to 90 years; 57% (541) of subjects were male and 42% (398) were female. Most subjects, (99%, n=928) were Caucasian, 1% (6) were black, and <1% (4) were Asian. Healthy volunteers were the youngest group, with a mean age of 55.9 years. Subjects diagnosed with DLB were the oldest, with a mean age of 73.5 years.

Disposition

**Table 3** summarizes the patient disposition by study. For study 003, 26 patients were not dosed mostly due to withdrawal of consent or protocol violations. Since the reference standard was based on referral information, all dosed patients were had reference evaluation; 220 of the 224 dosed patients had evaluable images. Of these 220 patients, 35 were healthy volunteers, which were not part of the primary efficacy evaluation. For study 004, 23 patients withdrew before dosing; 174 of the 179 dosed patients had evaluable images. Only 102 patients had the reference standard which occurred at 36 months. The majority of dosed patients without the 36-month standard of truth was lost to follow up or withdrew consent. For study 301, 23 patients withdrew before dosing. All dosed patients had reference evaluation; 313 patients have evaluable images. A total of 82 patients were excluded from the primary efficacy analysis, because of no diagnosis (26 patients) or a possible DLB diagnosis (56 patients). Comparison of demographics and diagnostic categories in efficacy population subgroups and the enrolled population showed that these two groups were similar.

**Table 3. Patient Disposition**

	<b>DP008-003</b>	<b>PDT3004</b>	<b>PDT 301</b>
Enrolled	250	202	351
Dosed	224	179	326
Reference Evaluated	224	102	326
Image Evaluable	220	174	313
Efficacy	220	102	313
Primary Efficacy	185	102	231

### Efficacy analyses

Average agreement between the Datscan images reads and the non-reference standard (clinical diagnosis) is shown in **Table 4**. Study 301 met its prespecified statistical threshold. For study 003 and 004 no thresholds were specified. Examination of individual reader performance showed an acceptable level of variability between readers.

**Table 4. Phase 3 Study Results, Average Positive and Negative Percent Agreement**

Outcome	Study		
	DP008-003 (movement disorder)	PDT3004 (movement disorder)	PDT301 (dementia)
Positive Percent Agreement	98%	78%	78%*
Negative Percent Agreement	98%	97%	90%*
N	220	101	224

\*p < 0.05 for primary endpoint hypothesis testing

With regard to study 003 the primary clinical reviewer identifies the following two important deficiencies:

- 1) The study enrolled patients with an established clinical diagnosis of PD, MSA, PSP or ET. Patients with established clinical diagnosis are not consistent with the proposed indicated patient population; such patients are likely to be more advanced in disease stage than patients being evaluated for symptoms and signs of a movement disorder
- 2) Lack of pre-specified statistical thresholds for success

The primary clinical reviewer's opinion regarding study 003 is that it is not acceptable as a confirmatory study, but provides supportive data for Datscan use in patients with Parkinsonian disorders.

With regard to study 004 the primary clinical reviewer emphasizes the following study strengths:

- 1) the population of subjects (early PS) reflects the population of patients likely to benefit most from Datscan imaging.
- 2) The reference procedure: expert clinical diagnosis at 36 month follow up is sufficiently rigorous

The primary clinical reviewer finds the study to be acceptable.

With regard to study 301 the primary clinical reviewer finds the following important deficiency: The reference procedure consists of baseline clinical diagnosis without follow up and is not reliable. In addition the diagnostic criteria used (1996 consensus criteria) further weaken the confidence in the clinical diagnosis. As a result the reviewer believes that study 301 does not qualify as a confirmatory study.

**Overview of Supportive Efficacy Studies**

Walker and colleagues have been studying eighty subjects with a clinical diagnosis of PS (PD or DLB), a non-PS disorder (Alzheimer’s disease) or no disorder (healthy volunteers). The subjects underwent Datscan imaging and are being followed until death, when a postmortem diagnosis is made and serves as the reference standard. To date, 23 subjects have undergone autopsy, and full data are available for 22 subjects (**Table 5**). The estimates of the sensitivity and specificity are: 78% and 85% for DaTSCAN and 78% and 46% for the clinical diagnosis at baseline.

The CDTL agrees with the primary reviewer that these numbers are difficult to interpret. Approximately 50% of the autopsied patients were found to have mixed pathology (e.g., DLB with Alzheimer’s disease (AD) cerebrovascular disease (CVD), or both), casting doubt on the reliability of clinical diagnosis of DLB. The criteria for clinical and pathologic diagnosis of DLB have been modified since the study began. No attempt has been made to date to quantify binding of ioflupane to various regions of the postmortem brain specimens. Finally the sample size is small and only four patients with PD have been evaluated to date. The CDTL reviewer agrees that these data do not provide substantial support to proposed use of Datscan and citation of the data in the package insert is not justified.

**Table 5. Baseline Clinical Diagnosis and Datscan Images by Neuropathological Results**

Neuropathological	Baseline Clinical Diagnosis		Datscan	
	DLB	Non-DLB	Abnormal	Normal
DLB	7	2	7	2
Non-DLB	7	6	2	11

**Safety**

A total of 942 study patients were evaluable for safety. **Table 6** shows the numbers of patients in each diagnosis group within the safety population. The duration of follow up was 7 days for study 003 and 2-3 days for study 301. For study 004 patients were followed by phone after each of the study visit at 0, 18 and 36 months.

**Table 6. Diagnosis Groups in the Safety Population**

Total safety population	Parkinsonism (PD,PSP, MSA)	Dementia with Lewy bodies	Essential tremor	Healthy volunteer	Other	Not known
942	409 (43) <sup>a</sup>	168 (18)	29 (3)	57 (6)	254 (27)	25 (3)

<sup>a</sup> numbers in parentheses are percentages

### Deaths

Five deaths occurred in the patients enrolled in the studies. None of the deaths are attributable to Datscan because of the timing of the events and the associated clinical conditions (malignancy, sepsis, heart failure, or traumatic fracture).

### Other adverse events

Overall, 588 adverse events were reported in 231 patients, and 73 (12%) of the events were considered by the investigator to be at least possibly related to Datscan administration. Among the 39 patients who experienced an event possibly related to Datscan, the most common were headache (n=13, 1%), nausea (n=8, <1%), and vertigo, dry mouth, hunger, and dizziness (3 each, < 1%).

### Discontinuations from study

A total of 10 (1%) subjects experienced an adverse event that led to discontinuation from the study. None of the events leading to discontinuations were attributed to Datscan.

### Clinical laboratory data

No clinically important changes in serum biochemistry or hematology values or urine analyses were observed. Urinalysis assessments including baseline and post-injection urine pH and specific gravity revealed no clinically significant changes from baseline. Summaries of shifts in values from baseline to post-injection did not reveal changes attributable to a drug effect.

### Vital signs and electrocardiograms

No clinically important changes in heart rate and blood pressure values were observed following the administration of Datscan. Summaries of shifts in values from baseline to post-injection did not reveal changes attributable to a drug effect. Among the 794 subjects with electrocardiographic assessments before and after Datscan administration no changes attributable to Datscan were identified.

### Dosimetry

Radiopharmaceuticals are associated with a risk of malignancy due to radiation exposure to the patient. Based on the dosimetry data the CDTL and the primary reviewer agree that the radiation exposure to patients at the proposed dose is acceptable.

The highest absorbed radiation dose following Datscan administration was seen in the urinary bladder wall (0.054 mGy/MBq), followed by the lungs (0.043 mGy/MBq), lower large intestine (0.042 mGy/MBq) and the upper large intestine (0.038 mGy/MBq). Dosimetry estimates using OLINDA software indicate the total effective dose to be approximately 3.94 mSV for an administered activity of 5 mCi. Given the long latency and high background rate of cancer it is not feasible to quantify the risk associated with the administration of Datscan. The package insert will need to cite the risk of malignancy.

### Postmarketing reports

The Sponsor estimates that up to July 2008, approximately (b) (4) patients had received Datscan. During this period the most clinically important spontaneous reports consist of five cases of severe pain on injection. One case of hypersensitivity reaction (non-serious) was reported. It is likely that rapid injection of the acidic formulation accounts for injection pain. The package insert will cite these reactions and will include a recommendation to inject slowly in a large vein.

The CDTL and the secondary reviewer agree that no clinically important safety signals have emerged to date from the clinical experience with Datscan.

## **7. Advisory Committee Meeting**

The Peripheral and Central Nervous System advisory committee supplemented with medical imaging experts met to discuss this NDA. The committee recommended that Datscan be approved.

## **8. Pediatrics**

A waiver was granted because nigrostriatal degeneration is a disease of adults.

## **9. Other Relevant Regulatory Issues**

None

## 10. Labeling

The reader is referred to the revised label recommended by the clinical, CMC, microbiology, and pharmacology reviewers for complete details of proposed label revisions.

The CDTL and primary reviewer recommend the following revisions to the clinical sections of the package insert (PI).

Change the indication statement from a “functional” to “structural” statement with emphasis on the adjunctive role of Datscan for visualization of the dopamine transporter in patients with symptoms and signs of a Parkinsonian syndrome.

Add the statement that Datscan is not indicated for screening, assessment of disease progression or response to treatment.

Omit the pooled presentation of the efficacy data. Present efficacy data for study 003 and 304 by study and by independent reader. Identify the clinical diagnosis as non-reference standard and provide positive and negative percent agreement of Datscan with the clinical diagnosis.

Omit mention of the Walker study.

Strike references to a training manual. Submit the manual when available as a labeling supplement to the NDA.

## 11. Recommendations/Risk Benefit Assessment

### Recommended Regulatory Action

From the clinical perspective the CDTL and the primary clinical reviewer agree that:

- the totality of the preclinical and clinical data show that Datscan allows visualization of the Dopamine transporter within the striatum in the brain,
- the available clinical data show a favorable risk benefit for the adjunctive use of Datscan in patients presenting with symptoms and signs of Parkinsonian syndrome.

The CMC, Toxicology and Pharmacology reviewers recommend an approval action.

The CDTL recommends approval of the NDA pending agreement by the applicant to revise the product’s package insert label as recommended by the NDA review team.

Recommendation for Postmarketing Risk Management Activities

There are limited and inconclusive clinical data available to assess the potential for interaction of Datscan with dopaminergic drugs. Therefore a drug-drug interaction study is recommended.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22454	----- ORIG 1	----- GE HEALTHCARE INC	----- DA TSCAN

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