

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022454Orig1s000**

**OTHER ACTION LETTERS**



NDA 022454

**COMPLETE RESPONSE**

GE Healthcare  
Attention: Allison Mueller  
Director, Global Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Mueller:

Please refer to your new drug application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DaTscan (Ioflupane I 123 Injection) for Intravenous Use.

We acknowledge receipt of your amendments dated March 25; April 16 and 22; May 20; June 19; July 7 and 29; August 11, 21, and 27; September 3 and 4; November 18; and December 17, 2009.

The October 26, 2009, amendment constituted a complete response to our September 8, 2009 action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

## **CLINICAL**

The proposed package insert (received on December 17, 2009) did not include the text necessary to support the approval of a controlled substance.

- a. Supply a revised label that incorporates this text.
- b. Alternatively, verify that this text does not apply to DaTscan, based upon findings from the Drug Enforcement Administration.

## **LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

## POSTMARKETING ISSUES

Several issues pertinent to clarifying the safety or efficacy of this product require additional information that may be obtained from postmarketing studies or clinical trials. We understand that you are refining your clinical development plans, in response to our letter of September 8, 2009. We reiterate our postmarketing requests from that letter. Specifically, we request that you propose studies and/or clinical trials to address the following issues:

- 1) To conduct a clinical trial that assesses the agreement between DaTscan imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients. The trial will be designated and conducted in a manner that allows a comparison of the results between the non-Caucasian and Caucasian patients.
- 2) To conduct a clinical trial that assesses the impact of dopaminergic drugs upon DaTscan results. In addition to any other drugs, levodopa and carbidopa effects should be studied in this trial.

Describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. Your response should include:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.
- The proposed schedule for conducting the study/clinical trial, including all major milestones for the study/clinical trial, e.g., submission to the FDA of the finalized protocol, initiation of an animal or clinical study, completion of patient accrual, completion of the study/clinical trial, and submission of the final report, with accompanying SAS datasets and applicable revised labeling.

## OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796- 2050.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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JAMES W MOORE  
12/23/2009

RAFEL D RIEVES  
12/23/2009  
On behalf of Dr. Pazdur



NDA 22-454

**COMPLETE RESPONSE**

GE Healthcare  
Attention: Allison Mueller  
Senior Manager, Regulatory Affairs  
101 Carnegie Center  
Princeton, NJ 08540-6231

Dear Ms. Mueller:

Please refer to your new drug application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DaTSCAN (Ioflupane I 123) Injection.

We acknowledge receipt of your submissions dated March 25, April 16 and 22, May 20, June 19, July 7 and July 29, August 11, 21 and 27, September 3 and 4, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

## CLINICAL

1. The proposed package insert (received on September 3, 2009) contained several items that require clarification, justification or redevelopment. Supply information and a revised package insert that addresses the following items:
  - a. The proposed indication does not clearly define "Parkinsonian syndromes (PS)" and appears promotional in tone. Redevelop the proposed indication statement to clearly define PS and to delete the phrase that notes, (b) (4). We supplied a draft "indication" proposal to you on September 1, 2009, that contained the items we regarded as important for your labeling. Several aspects of our proposal were not incorporated into your subsequent revision and your deletions were inadequately justified. Redevelop the "indication" statement within your proposed package insert to address the items cited in our September 1, 2009, proposal.
  - b. With respect to the "Thyroid Blockade" portion of your September 3, 2009, proposed package insert, you have stated that (b) (4). Your original proposal stated that prescribers should, (b) (4). Summarize the "thyroid blocking"

procedures used in your clinical trials and those currently recommended within your marketing experience outside the United States.

- c. The "Image Interpretation" section of your proposed package insert notes that, (b) (4)  
[REDACTED] Justify this contention, based upon your clinical trial experience and describe your plans for the development of any "instructional manuals" or other documents intended to assist in "Image Interpretation." Supply a copy of these documents.
- d. Justify your decision to delete the following statement from your package insert, "Failure to block thyroid uptake of iodine 123 may result in an increased long term risk for thyroid neoplasia." Consider other marketed radioactive iodine-containing products.
- e. Your September 3, 2009, submission contained new data and information that was supplied following completion of our review. This information (pertaining to the use of DaTSCAN among nursing mothers) will be reviewed following your response to this letter. To facilitate this review, we encourage you to highlight the basis for your "Nursing Mothers" proposal within your response.
- f. Justify your contention that, (b) (4)  
[REDACTED]
- g. Regarding the "Clinical Studies" section of the package insert:

Revise this section within your subsequent submission to address the items you deleted from our September 1, 2009 package insert proposal. In particular, we object to the pooling of data across readers, the use of the terms (b) (4) and the inclusion of healthy volunteers in the Study 2 summaries. Additionally, justify the deletion of the statement that noted, "Study 1 readers had no other role in patient assessment; Study 2 readers included the investigators." We disagree with your overall approach that appears to support the use of DaTSCAN as a test with greater clinical impact than is consistent with the available clinical trial data. We described the many limitations with your clinical trials at the August 11, 2009 Advisory Committee presentation and we regard these limitations as also limiting the ability to describe performance characteristics within your package insert.

2. Contingent upon your response to the labeling items listed above, we may request additional information or further label revisions.

## **LABELING**

We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

## **SAFETY UPDATE**

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Richard Pazdur, M.D.  
Director  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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JAMES W MOORE  
09/08/2009

RICHARD PAZDUR  
09/08/2009