

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022454Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-454
From: Sarah C. Pope, Ph.D.
Date: 9/8/2009
Re: Final CMC recommendation for NDA 22-454

NDA 22-454 was initially submitted on 09-MAR-2009 and was granted a priority review by the Agency. Chemistry Review #1 (02-SEP-2009) resulted in a recommendation for approval pending a determination of acceptability from the Office of Microbiology. At the time of CMC review finalization, the microbiology review was not yet final.

This memo serves to update that determination. The Office of Microbiology (Dr. B. Riley) issued a recommendation for approval in a review dated 31-AUG-2009.

With the exception of very minor labeling changes, which will be captured in the final approval letter, all CMC deficiencies have been resolved, and there are no outstanding issues with this NDA. Therefore, approval of NDA 22-454 is recommended from a CMC perspective.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22454

ORIG-1

GE HEALTHCARE
INC

DA TSCAN

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/s/

Sarah Pope Miksinski
09/08/2009

ONDQA Division Director's Memo
NDA 22-454, DaTSCAN™, [¹²³I] ioflupane 2mCi/mL (5 mCi/vial) at calibration time
intravenous injectable suspension
Date: 02-SEP-2009

Radiopharmaceutical

Introduction

DaTSCAN™, [¹²³I] ioflupane 2mCi/mL (2.5 mL/vial provides 5 mCi/vial at calibration time), is a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous injection. DaTSCAN will be used as an imaging agent for imaging of dopaminergic neurons by single photon emission computed tomography (SPECT). The drug product is supplied as a clear colorless solution in a 10 mL single use vial.

Administrative

The original submission of this 505(b)(1) NDA was received 06-MAR-2009 from GE Healthcare, Princeton, MA. Three amendments were received and reviewed after the original submission; as late as 27-AUG-2009.

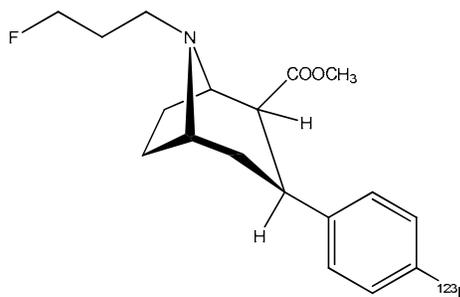
A satisfactory EES recommendation was provided on 15-JUL-2009

There are **no outstanding CMC deficiencies from ONDQA**. However, the Microbiology review is pending as of this writing. Thus, **ONDQA's recommendation for APPROVAL is pending a satisfactory outcome from the Product Quality Microbiology review**.

Drug Substance ([¹²³I] ioflupane)

DaTSCAN contains the radioiodinated tropane analog, ioflupane I 123. Chemically, ioflupane I 123 is "methyl (1R-2S-3S-5S)-8-(3-fluoropropyl)-3-(4-[¹²³I]iodophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate". (b) (4)

. Based on specific activity considerations, the 5 mCi dose in 2.5 mL volume will contain a maximum of 0.33 mcg of ioflupane (both radioactive and non-radioactive).



Chemical Formula: C₁₈H₂₃F¹²³INO₂
Molecular Weight: 427.28

Elemental Analysis: C, 50.60; H, 5.43; F, 4.45; I, 28.76; N, 3.28; O, 7.49

The I-123 radioisotope is cyclotron-produced with a physical half-life of 13.2 hours, which decays to Te 123 by electron capture with the emission of gamma radiation (159 keV).

Drug Product (DaTSCAN™, [¹²³I] ioflupane 2mCi/mL)

The drug product contains 2.5 mL in a 10 mL single-use vial.

Each milliliter contains 0.07 to 0.13 mcg ioflupane, 2 mCi (74 MBq) 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. Each single use vial contains 185 MBq (5 mCi) of ioflupane I 123 drug. Each vial is enclosed in a lead container of appropriate thickness.

Rik Lostritto, Ph.D., Director, ONDQA Division III

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

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/s/

RICHARD T LOSTRITTO
09/02/2009

NDA 22-454

**DaTSCAN™
(Ioflupane I 123 Injection)**

**GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540-6231**

**Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Division of Premarketing Assessment and
Manufacturing Science
Branch V, ONDQA
CDER, FDA**

**For The Division of Medical Imaging and Hematology
Products**

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Chemistry Review Data Sheet

1. NDA 22-454
2. REVIEW #: 1
3. REVIEW DATE: 25-Aug-2009 (revised / updated 02-Sep-2009)
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

06-March-2009

Amendment (BZ)

22-Jun-2009 (19-Jun-2009 letter)

Amendment (BC)

25-Jun-2009 (19-Jun-2009 letter)

Amendment (LR)

27-Aug-2009

A. NAME & ADDRESS OF APPLICANT:

Name: GE Healthcare

Address: 101 Carnegie Center, Princeton, NJ 08540-6231

Representative: Allison Muller, Director Regulatory Affairs

Telephone: 609-514-6843

A. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: DaTSCAN™

b) Non-Proprietary Name (USAN): [¹²³I] ioflupane (INN and BNN)c) Code Name/# (ONDC only): [¹²³I]FP-CIT, [¹²³I]β-CIT-FP

d) Chem. Type/Submission Priority (ONDC only):

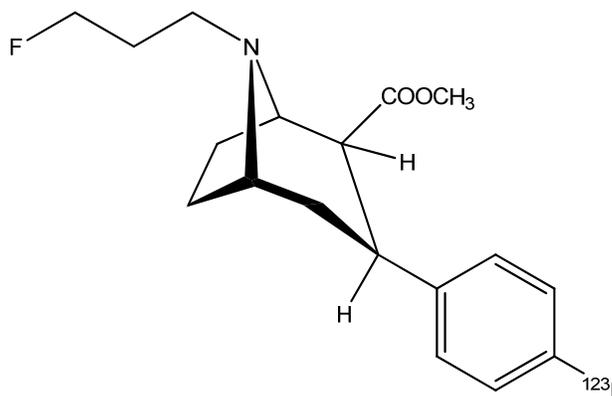
- Chem. Type: 1
- Submission Priority: P

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Radiopharmaceutical
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 2mCi/mL (5 mCi/vial) at calibration time
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product

A. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- Chemical name IUPAC: Methyl (1R, 2S, 3S, 5S)-8-(3-fluoropropyl)-3-(4-[¹²³I]iodophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate
- Trivial Chemical Name: N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[¹²³I]iodophenyl) nortropane



Chemical Formula: C₁₈H₂₃F¹²³INO₂

Molecular Weight: 427.28

Elemental Analysis: C, 50.60; H, 5.43; F, 4.45; I, 28.76; N, 3.28; O, 7.49

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS

Chemistry Review Data Sheet

(b) (4)	7			Review by microbiology Reviewer
	3	Adequate	26-Oct-2000	A. Mueller, Ph.D.
	1, 3	Adequate	Sep-2009	Ravindra K Kasliwal, Ph.D., Coating reviewed previously by Mark Sassarman, Ph.D.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	101,016	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	15-Jul-2009	E. Johnson
Pharm/Tox	Pharmtox is acceptable. No consult was requested.		
Biopharm	N/A		
LNC	N/A		
Methods Validation	No methods validation requested.		
ODA	Trademark is acceptable		Denise V. Baugh, Pharm.D.
EA	Categorical exclusion recommended - Acceptable	Date of this review	Ravindra K. Kasliwal, Ph.D.
Microbiology	Pending		Bryan Riely, Ph.D

The Chemistry Review for NDA 22-454

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act. The Office of Compliance recommends (15-Jul-2009) that the manufacturing facilities are acceptable. The following should be verified prior to approval of the drug product application:

- Product quality microbiology has found the application to be approvable.
- The labeling comments sent to the company have been incorporated in the labels.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DaTSCAN (Ioflupane I 123 Injection) is a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous injection. The I-123 radioisotope is cyclotron-produced with a physical half-life of 13.2 hours, which decays to Te 123 by electron capture with the emission of gamma radiation (159 keV). The product is supplied clear and colorless solution in a 10-mL single use glass vial closed with a rubber stopper and sealed with an aluminum cap. Each milliliter contains 0.07 to 0.13 mcg ioflupane, 2 mCi (74 MBq) 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. Each single use vial contains 185 MBq (5 mCi) of ioflupane I 123 drug. Each vial is enclosed in a lead container of appropriate thickness.

DaTSCAN contains the radioiodinated tropane analog, ioflupane I 123. Chemically, ioflupane I 123 is "methyl (1R-2S-3S-5S)-8-(3-fluoropropyl)-3-(4-[¹²³I]iodophenyl)-8-azabicyclo[3.2.1] octane-2-carboxylate". (b) (4)

Based on specific activity considerations, the 5 mCi dose in 2.5 mL volume will contain a maximum of 0.33 mcg of ioflupane (both radioactive and non-radioactive).

B. Description of How the Drug Product is Intended to be Used

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 (calibration) time and date. Each Package contains one vial with 2.5 mL of solution containing 2.0 mCi / mL ioflupane I 123 drug at the time of reference. No other manipulations to the drug product are needed or recommended prior to its administration through intravenous route. The recommended dosage of 3 to 5 mCi requires administration of 1.5 mL to 2.5 mL volume.

DaTSCAN will be used as an imaging drug for imaging of dopaminergic neurons by single photon emission computed tomography (SPECT). To minimize the potential for pain at the injection site during administration, a

Executive Summary Section

slow intravenous injection (not less than 15 to 20 seconds) via an arm vein is recommended. The patient is imaged between 3 and 6 hours following administration of the drug product.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval action for CMC based on that, (1) the CMC have been satisfactorily addressed, (2) acceptable cGMP recommendation on manufacturing facility has been received from the CDER Office of Compliance (3) provided pending labeling issues are satisfactorily addressed, (4) the Office of Drug Safety has found trademark "DaTSCAN" to be acceptable, if "-TSCAN" part is in lower case and (5) pending acceptability of the product quality microbiology.

III. Administrative

A. Reviewer's Signature: *Rgvindra K. Kasliwal, Ph.D.*

B. Endorsement Block

Kasliwal/Date: 02-Sep-2009
Leutzinger/ 02-Sep-2009
Pope Miksinski / 02-Sep-2009

C. CC Block : See DARRTS

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

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/s/

RAVINDRA K KASLIWAL
09/02/2009

ELDON E LEUTZINGER
09/02/2009

Sarah Pope Miksinski
09/02/2009

Initial Quality Assessment (IQA)
Branch V

Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division: DMIHP

NDA: 22-454

Applicant: GE Healthcare, 101 Carnegie Center, Princeton, NJ 08540

Stamp Date: March 9, 2009

PDUFA Date: TBD, pending whether priority or standard

Trademark: DaTSCAN

Established Name: Ioflupane I 123 Injection

Dosage Form: Sterile solution

Route of Administration: IV

Indication: "DaTSCAN is a radiopharmaceutical [¹²³I]ioflupane, indicated 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."

Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D.

YES NO

ONDQA Fileability:

 X ¹

Comments for 74-Day Letter (Not at this time, and awaits start of formal review)

(1) Based on this initial review, the application is largely substantively complete, sufficiently organized and legible for the start of formal review. The only absence found was that of the readiness of the manufacturing facilities for inspection, either in 3.2, or in the introductory section. The firm should be contacted at this time for that information, so that the request for inspections can be now entered. Also, this information should be requested provided to 3.2 (Quality). Unless it is learned that these sites are not ready at this time, the application is fileable from a CMC standpoint.

Summary and Critical Issues:

A. Summary

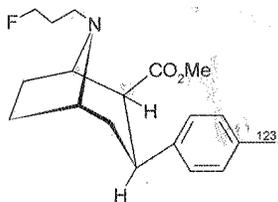
NDA 22-454 is a new NDA for DATSCAN, the drug molecule of which has not been approved or marketed as the active moiety in the United States in any drug product, either as a single ingredient, as part of a combination product, or as part of a mixture of stereoisomers. As such, and in accordance to the Drug and Application Classification system, the active moiety in NDA 22-454 is an NME (Type 1).

DaTSCAN (Ioflupane I 123 Injection) is a ready-to-use sterile solution packaged in 10 mL Type 1 glass vials with (b) (4) rubber closure (Drug Product). Each mL of the formulation contains 74 MBq (2 mCi) of [¹²³I]ioflupane at reference time, (b) (4) of ioflupane (b) (4) 0.05 mL of ethanol and (b) (4) with sodium acetate (b) (4)

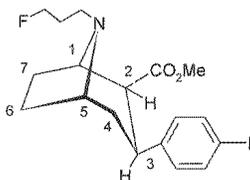
(b) (4) of acetic acid (b) (4)
Due to the short physical half-life of I (13.2 hours).

The compatibility of drug product with 6 commercially available disposable plastic syringes were evaluated; these study results are discussed in the section on Pharmaceutical Development. Based on stability results (3 batches), drug product is given an expiration of 7 hours from reference (b) (4). Drug product (formulation and container closure) manufactured for use in the clinical studies was identical to that proposed for marketing.

The Drug Substance is [¹²³I]ioflupane, the full chemical name (trivial) of which N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[¹²³I]iodophenyl)nortropane. Its IUPAC name is methyl (1R, 2S, 3S, 5S)-8-(3-fluoropropyl)-3-(4-[¹²³I]iodophenyl)-8-azabicyclo[e.2.1]octane-2-carboxylate, and has the following chemical structure.



The drug substance molecule, [¹²³I]ioflupane, is optically active, consisting of 4 chiral centers, just as for [¹²⁷I]ioflupane, below and with the numbering system as shown.



The 1R, 2S, 3S, 5S-isomer is chosen because of the known pharmacological activity of natural (1R)-cocaine and its derivatives. (b) (4)

B. Critical Issues for Review

Stated is that product (formulation and container closure) that was used in the clinical studies was the same as that proposed for marketing. The reviewer needs to verify this (Critical Issue #1). An initial review of the (b) (4) report on the preparation and characterization of [¹²⁷I]ioflupane did not reveal anything regarding structural elucidation itself that was immediately concerning. However, there are some potential issues regards reference standards. The current Working Reference Standard batch for [¹²⁷I]ioflupane (FP-CIT) is identified as FFC0005/071-03. GE has listed acceptance criteria for FP-CIT (3.2.S.5-ref-standards-materials), and it is presumed that this list was generated based on the characterization of a Primary Reference Standard, so that there will be an established link between all working standards used in routine quality control and the original material that underwent the formal structural studies. I consider this very important, since reference standard implies authenticity, so that comparisons with the standard resst on a sound basis. This is Critical Issue #2.

Section 3.2.P.5.1 (release specifications for drug product) indicates that Radiochemical Identity is determined by TLC by radiochromatogram scanning (relative retention time: 0.8 – 1.0). The same TLC procedure is used in the stability studies. The procedure used for both RCID and RCP appears to be validated (USHM-VLD-08-054; Section 3.2.P.5.3). A chromatogram of a test mixture of (b) (4) (an impurity), (b) (4) (another impurity) and ioflupane shows all 3 peaks well separated; no interference in assessment of ioflupane by impurities was evident. There is no reason why TLC/radiochromatogram scanning is necessarily inferior to HPLC, although from an analytical standpoint, HPLC is generally considered superior to TLC. There is a good discussion of impurities (theoretical and actual), Section 3.2.S.3.2, and HPLC was used in assessment of what impurities are present (b) (4). It is not clear whether any of these would be, or are found in the final product by carry over; the levels are relatively small in (b) (4), and might not present any concerns if they were carried over. The results from HPLC studies were obviously used in assessment of the suitability of TLC for QC release of final product from the aspect of both potential and actual impurities observed. Although their several arguments have merit (theory), what I am concerned about is that there is no ‘confirmation’ that TLC would do as well as HPLC, i.e., having carried out an actual comparison between TLC and HPLC. This is Critical Issue #3.

GE is saying that radiochemical stability of the drug product was (b) (4) 7 hours after reference (b) (4). The expiration is set at 7 hours post reference (calibration). That puts the expiration point (b) (4). I did not immediately see anything seriously amiss in this initial review with stability and setting an acceptable expiration dating period. However, the reviewer needs to examine these considerations very carefully. This is Critical Issue #4. A reasonably good discussion of impurities was found in Section 3.2.S.3.2 (referred from Section 3.2.P.5.5). Various potential and actual impurities are discussed, and I did not see anything from an initial review that was of immediate concern. The reviewer will, of course, need to review this section in greater detail.

C. Comments for 74-Day Letter

Not a full enumeration of issues at this time.

Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?		X	Was not found in the initial review
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		
7.	Does the section contain controls for drug substance?	X		(b) (4)
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		There is a section on formulation development (3.2.P.2.2.1), indicating (Section 3.2.P.2.2.2) that the composition of product for clinical trials and container closure were identical with product proposed for marketing. Appears to be a “one-time” decision on formulation, as opposed to a progression of formulations leading to the one proposed for marketing.
13.	Has the applicant provided a method validation package?	X		
14.	Is a separate microbiological section included?	X		Section 3.2.P.2.5

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
		(b) (4)	X		
			X		
			X		

Production Facilities for Drug Substance			
Facility	Address	Responsibility	CGMP Inspection Needed
GE Healthcare AS	Nycoveien 1-2 0485 Oslo, Norway (Contact: Anne Katrin Haga, Director QA R&D, Telephone: 0114723185488 FAX: 0114723186009 anne.katrin.haga@ge.com) FEI# FCN0085	(b) (4)	TBD
GE Healthcare	3350 N Ridge Ave Arlington Heights, IL 60004 (Contact: Erik Datisman, QA Site Lead, Telephone: 1-847-385-5488 FAX: 1-847-385-5488 erik.datisman@ge.com) FEI# 1417338	(b) (4)	No ¹
GE Healthcare	Same as indicated at Arlington Heights, IL	Manufacture of drug product, processing, testing, packaging, labeling	X

(b) (4)



Consults To Be Initiated	
Item	Consult To
1. Microbiology sections (3.2.P.2.5)	Microbiology Staff

Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D. Date: 03/30/2009

Branch Chief: Sarah Pope, Ph.D. Date:

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this page is the manifestation of the electronic signature.**

/s/

Eldon Leutzinger
3/30/2009 09:06:50 AM
CHEMIST

Sarah Pope
3/30/2009 03:06:34 PM
CHEMIST