CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200655Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	200655
Supporting Document #	37
PDUFA Goal Date	June 15, 2016
OSE RCM #	2016-10
Reviewer Name(s)	Mona Patel, Pharm.D.
DRISK Team Leader	Naomi Redd, Pharm.D., Team Leader
Division Director	Cynthia LaCivita, Pharm.D., Division Director
Office Director	Claudia Manzo, Pharm.D., Director, Office of Medication Error Prevention & Risk Management
Review Completion Date	May 8, 2016
Subject	Evaluation to determine if a REMS is necessary
Established Name	[F-18] Fluorodopa (FDOPA)
Applicant	The Feinstein Institute for Medical Research
Therapeutic Class	Radiopharmaceutical
Formulation	Injection
Dosing Regimen	(b) (4) 5.0 mCi ((b) (4) 0.185GBq)administered intravenously

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Fluorodopa is necessary to ensure the benefits of this product outweigh its risks. The Feinstein Institute of Medical Research submitted a New Drug Application (NDA 200655) for Fluorodopa with the proposed indication as a radioactive diagnostic agent for positron emission tomography (PET) to (b) (4) .

As with other radiopharmaceuticals, the potential risks associated with the use of Fluorodopa are radiation exposure and allergic reactions; however there were no observed serious adverse events due to Fluorodopa observed in the studies supporting this application. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK does not recommend a REMS to ensure the benefits of Fluorodopa outweigh its risks. The potential risks with this drug will be communicated through labeling.

1 Introduction

The Feinstein Institute of Medical Research submitted a New Drug Application (NDA) for Fluorodopa with the proposed indication as a radioactive diagnostic agent for positron emission tomography (PET) to (b) (4) .

This application is under review in the Division of Medical Imaging Products (DMIP). The applicant did not submit a REMS with this application but proposed risk minimization measures that included product labeling.

2 Background

2.1 PRODUCT INFORMATION

Fluorodopa is a diagnostic radiopharmaceutical and is not used to treat any disease or medical condition. This product undergoes decarboxylation in the brain by aromatic amino acid decarboxylase (AAAD) in the striatum to F-18 fluorodopamine (FDA) and subsequently to [^{18}F] 6-fluoro-3,4-dihydroxyphenylacetic acid (^{18}FDOPAC) and subsequently by catechol-O-methyltransferase (COMT) to yield [^{18}F] 6-fluorohomovanillic acid (^{18}FHVA).[1] The applicant's proposed indication for Fluorodopa is positron emission tomography (PET) to (b) (4)

(b) (4)

(b) (4)

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The recommended radioactivity to be administered is intravenous by a (b) (4) through a catheter inserted into a large peripheral vein of 5mCi. Imaging is to begin (b) (4) minutes after the injection and images are to be acquired (b) (4) minutes.[1] Fluorodopa is supplied in multi-dose septum capped 20 mL glass vial containing between 0.0155 – 0.3082 GBq of Fluorodopa F 18, 12.72 ug acetic acid and 108 mg sodium chloride in 12 mL sterile water for injection. The total half-life of the product is 109.7 minutes.[1] Patients are encouraged to avoid high protein food 4-6 hours prior to the intravenous administration of Fluorodopa (b) (4) All patients will be given 150 mg carbidopa one hour prior to the administration of Fluorodopa. Patients are also encouraged to void several times for (b) (4) hours immediately after the scanning ends.

This is a Class 2 Resubmission, 505 (b)(2) application, to address the serious design and conduct issues of the previous studies submitted in the original application, that relies in part on data from the approximately 22 independent literature reports that were submitted in the original 505b(2) application dated October 30, 2009and a prospective clinical study that was submitted in this resubmission (Study 17) for evidence of safety and efficacy of Fluorodopa in the proposed indication. There is no approved marketing application in the US for Fluorodopa. Fluorodopa is licensed in Europe including the United Kingdom, France, and Spain as Dopacis and IASOdopa This resubmission is under a six month review clock with a PDUFA date of June 15, 2016.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208054 relevant to this review:

- 10/30/09 New Drug Application Received
- 3/19/10 Refuse to File
- 10/22/12 Resubmission Following Refuse to File
- 10/22/13 Complete Response Letter
- 12/15/15 Class 2 Resubmission Received
- PDUFA Date: June 15, 2016

3 Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Parkinsonian syndrome or Parkinsonism is characterized by tremor, bradykinesia, rigidity, and postural instability. Parkinsonism shares symptoms found in Parkinson's disease, from which it is named; but

parkinsonism is a symptom complex, and differs from Parkinson disease which is a progressive neurodegenerative illness.[2]

3.2 DESCRIPTION OF CURRENT DIAGNOSTIC OPTIONS

Although no other drug has been approved for the proposed indication of "visualizing dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes," DaTscan (ioflupane I 123) was approved by the FDA in 2011 for a similar indication.[3] Ioflupane I 123 is indicated for striatal dopamine transporter visualization by SPECT brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes. In these patients, Ioflupane I-123 may be used to help differentiate essential tremor from tremor due to Parkinsonian syndromes (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy).

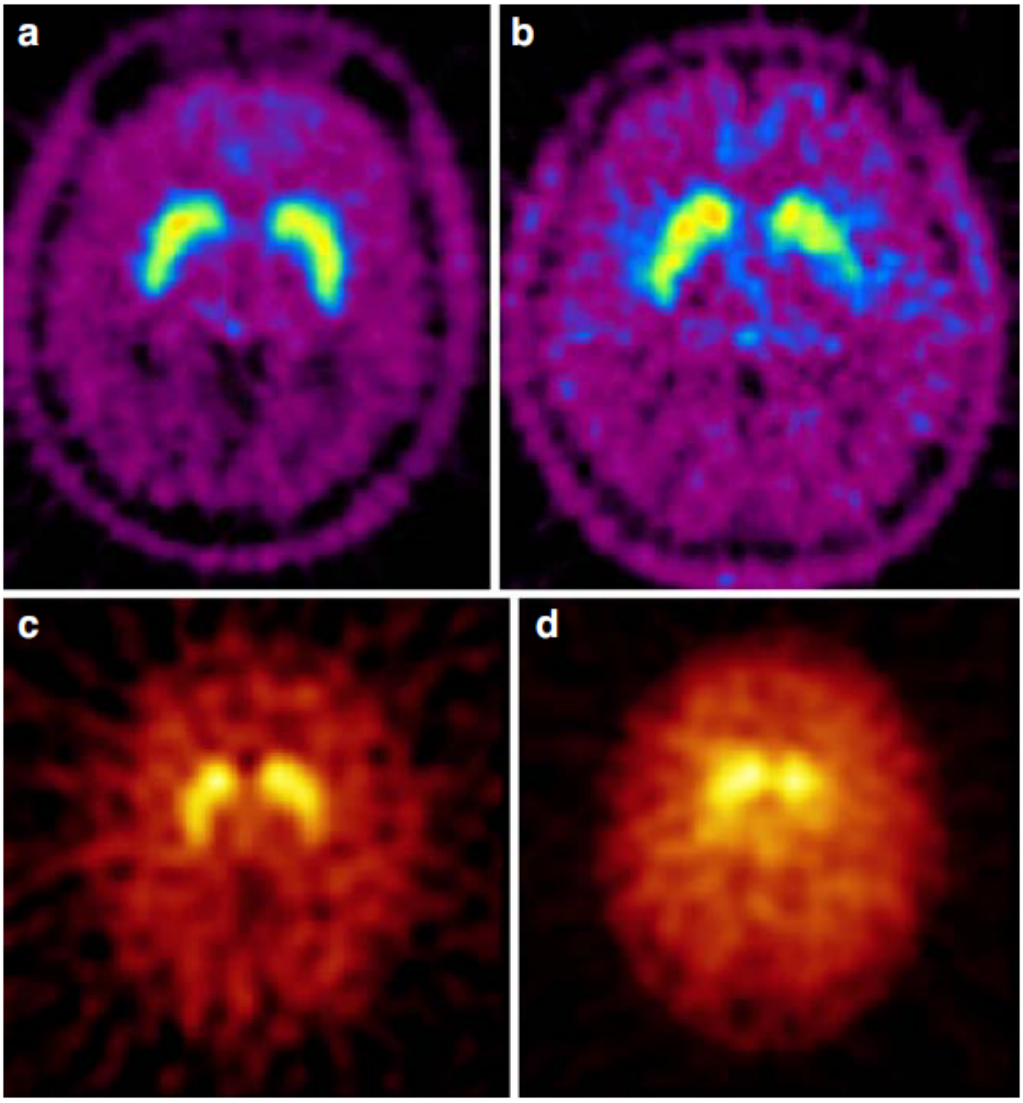
The long half-life (approximately 110 minutes) makes Fluorodopa practical for clinical use.

Figure 2 compares Fluorodopa PET images (panels a and b) with Ioflupane 123 SPECT images (panels c and d) in both healthy controls and patients with Parkinson Disease (PD).[4]

[2] Feinstein Institute for Medical Research October 29, 2009 New Drug Application Submission

[3] DatScan (Ioflupane I 123) US Prescribing Information 9/2015

[4] June 21, 2013 Clinical Review by Brenda Q. Ye



Limiting factors with the use of ioflupane I 123 is the need for patients to swallow a Potassium Iodide solution, Lugol's Solution or potassium perchlorate before administration of ioflupane I 123. Patients have a longer delay to start imaging with ioflupane having to wait 3 to 6 hours versus (b) (4) minutes with Fluorodopa.[3]

4 Benefit Assessment

The evidence of clinical benefit for Fluorodopa is primarily based on approximately 22 independent literature reports that were submitted in the original 505b(2) application dated October 30, 2009 and a prospective clinical study that was submitted in this resubmission, Study 17, that was conducted under the Expanded Access IND 78861.[4] Study 17 was a single arm study designed to evaluate the sensitivity, specificity, and usefulness of Fluorodopa for patients with suspected cases of Parkinsonian syndromes. A total of 45 patients were given Flurodopa PET scans in Study 17. The dose in this study was 4.05-5 mCi.

The primary endpoint in this study was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: “loss”/ “no loss.” Out of the 45 patients, 32 had positive PET scans and 13 had negative PET scans.[5] Based on the clinical review, it appears the combined studies support the effectiveness of Flurodopa in visualizing dopaminergic neuronal loss in patients with Parkinsonian syndromes. This will be further determined after review by a Special Government Employee.

5 Risk Assessment & Safe Use Conditions

There were no serious adverse events or deaths reported with the use of Fluorodopa and the possibility of interactions with other drugs taken by patients undergoing PET imaging has not been studied.[4,5]

The applicant proposed to include in the Warnings and Precautions section of the label, similar language that is found in all radiopharmaceuticals with limiting the exposure of radiation to the patient as much as possible (b) (4). Labeling meetings had not begun yet to evaluate the Warnings and Precautions section of the label.

Ioflupane I 123 has a similar safety profile but also has a potential risk of thyroid accumulation of the free iodide.[3]

6 Expected Postmarket Use

Diagnostic radiopharmaceuticals are limited to inpatient settings and are prepared and administered by nuclear medicine physicians and staff with appropriate radiation training. Like other imaging drugs, Fluorodopa will be administered by healthcare providers and other staff skilled and experienced in handling radiopharmaceuticals and the risks associated with taking these products.

7 Evaluation of Need for a REMS

As with other radiopharmaceuticals, the potential risks associated with the use of Fluorodopa are radiation exposure and allergic reactions. There were no observed serious adverse events due to Fluorodopa observed in the studies supporting this application. Ioflupane I 123 is a similar FDA-approved product to assist in the evaluation of adult patients with suspected Parkinsonian syndromes and has a similar safety profile but is also associated with the potential for thyroid accumulation to the free iodide.

Both of these products are given as a single IV dose for diagnostic use. No serious adverse effects were reported for either products in clinical trials.[1,3] However, with ioflupane I 123, there was a risk for accumulation of iodine 123 in the thyroid.

As with other diagnostic radiopharmaceuticals, Fluorodopa will be restricted to inpatient settings. This product will be prepared and given by nuclear medicine physicians and staff who are required to have

[5] April 22, 2016 Clinical Review by Brenda Q Ye

specialized training for the handling and management of radionucleotides as part of their daily clinical practice.

As a class, diagnostic radiopharmaceuticals do not have a Boxed Warnings in their respective labels and have not required a REMS to ensure the benefits outweigh the risks.

8 Risk Management Activities Proposed by the Applicant

The Feinstein Institute for Medical Research did not propose any risk management activities for Fluorodopa beyond routine pharmacovigilance and labeling.

9 Conclusion & Recommendations

In conclusion, DMIP and DRISK agree that risk mitigation measures beyond professional labeling are not warranted for Fluorodopa to ensure the benefits outweigh the risks. Healthcare providers who use radiopharmaceuticals are familiar with the risks associated with these products and understand the importance of patient monitoring. At the time of this review, evaluation of safety information and labeling was still ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile.

10 Appendices

10.1 Materials Reviewed

- Feinstein Institute of Medical Research Proposed Labeling for Fluorodopa March 23, 2016
- Feinstein Institute for Medical Research October 29, 2009 New Drug Application Submission
- DatScan (Ioflupane I 123) US Prescribing Information September 2015
- Feinstein Institute for Medical Research December 15, 2015 Resubmission
- June 25, 2013 DRISK Review by Amarilys Vega

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/s/

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05/08/2016

CLAUDIA B MANZO
05/09/2016
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	June 24, 2013
Reviewer(s):	Amarilys Vega, MD, MPH, Medical Officer, Division of Risk Management (DRISK)
Team Leader	Cynthia LaCivita, PharmD, Team Leader, DRISK
Division Director	Claudia Manzo, PharmD, Director, DRISK
Drug Name(s):	Fluorodopa F-18 Injection
Therapeutic Class:	Radiopharmaceutical (diagnostic imaging agent for Positron Emission Tomography (PET))
Dosage and Route:	(b) (4) 5.0 mCi ((b) (4) 0.185GBq)/intravenous
Application Type/Number:	NDA/200655
Applicant/sponsor:	Thomas Chaly, Ph.D., FAIC, Associate Professor, Chief, Cyclotron/Radiochemistry, The Feinstein Institute for Medical Research, New York
OSE RCM #:	2012-2513

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1. INTRODUCTION

This document is to defer DRISK's comments on the management of the risks associated with Fluorodopa F-18 for injection, new drug application (NDA) 200655.

1.1. Background

Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations. The drug product is provided in a multi-dose vial containing 0.42-8.33 mCi/mL (0.0155-0.3082 GBq/mL) at the end of synthesis (EOS) reference time. Fluorodopa F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous injection.[2]

This NDA is sponsored by Thomas Chaly, Ph.D., FAIC, Associate Professor, Chief, Cyclotron/Radiochemistry, The Feinstein Institute for Medical Research, New York.

1.2. Materials Reviewed

Following is a list of the materials reviewed.

- FDA refusal to file memo from October 19, 2010
- NDA submission from October 22, 2012
- NDA Mid-cycle meeting slide presentations, March 18, 2013
- FDA Mid-cycle communications to sponsor - March 25, 2013 teleconference meeting minutes
- Robert J. Mello, Ph.D., Product Quality Microbiology Review, dated June 4, 2013.
- Brenda Ye, M.D., Clinical Review, dated June 20, 2013.

1.3. Regulatory History

The regulatory history, in pertinent part, is as follows:

- **October 29, 2009:** FDA receives new drug application (NDA) for Fluorodopa [F-18] Injection (FDOPA).
- **March 19, 2010:** FDA issues a refuse to file letter due to multiple deficiencies (administrative, clinical, pharmacology/toxicology, and clinical pharmacology)
- **October 22, 2012:** NDA resubmitted to FDA
- **March 18, 2013:** Mid-cycle review meeting.
- **March 25, 2013:** Mid-cycle teleconference with the sponsor

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[1] Brenda Ye, M.D. DMIP Medical Officer, Midcycle meeting slide presentation, March 18, 2013.

[2] Fluorodopa F-18 Module 2 Summaries, page 4.

- **March 27, 2013:** Mid-cycle communication from FDA to sponsor. This communication included minutes from the March 25 teleconference with the sponsor. Key points communicated to the sponsor include the following:
    - Clinical and Statistical: ongoing review of the clinical data suggests that the submitted information provides insufficient evidence of efficacy. Of important concern is that the data reflect a single site experience and that the Standard of Truth in the main clinical study consists of a pre-imaging clinical diagnosis.
    - Microbiology:
        - Endotoxin testing: (1) the release of the product and its possible administration to the patient before completion of the test for bacterial endotoxins; (2) if the test fails, the lack any investigation as to why the test failed.
        - Sterility testing: (1) timing of testing, (2) actions in the event of a sterility test failure.

2. REVIEW FINDINGS

Due to outstanding microbiology, chemistry, statistical, and clinical deficiencies, the Division of Medical Imaging Products (DMIP) plans to issue a Complete Response (CR) letter. No safety data was submitted in the NDA. The Applicant states that there have been no safety concerns from over 20 years of use of the Fluorodopa F-18 at the Feinstein Institute.

3. CONCLUSION AND RECOMMENDATIONS

Based on the review of clinical data submitted, the efficacy and safety of Fluorodopa F-18 for injection for used in PET scans to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes cannot be established.

Until the efficacy and safety profile of Fluorodopa F-18 is established, the benefits and risks of Fluorodopa F-18cannot be adequately weighed and an appropriate risk management strategy cannot be determined. The Division of Medical Imaging Products plans to issue a Complete Response letter. Therefore, DRISK defers comment on the management of the risks associated with Fluorodopa F-18 and labeling at this time.

A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response letter.

Please notify DRISK if you have any questions.

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