CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-870

CHEMISTRY REVIEW(S)

NDA 21-870

Fludeoxyglucose F 18 Injection

North Shore/LIJ Health System
Institute for Medical Research
Cyclotron/PET facility
(Thomas Chaly, Ph.D., FAIC)

Milagros Salazar, Ph.D.
DNDC-II, ONDC
Division of Medical Imaging and Radiopharmaceuticals
Drug Products, OND

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-870

2. REVIEW #: 1

3. REVIEW DATE: 20-Jun-2005

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document date
Original	05-Nov-2004
N-000 C	10-Jan-2005
Amendment N-000 BC	08-Feb-2005
N-000 C	15-Mar-2005
N-000 C	28-Mar-2005
Amendment N-000 BL	26-May-2005
Amendment N-000 BC	15-Jun-2005
Amendment N-000 BI	29-Jun-2005
Amendment N-000 BI	30-Jun-2005
Amendment N-000 BC	05-Jul-2005
Amendment N-000 BC	21-Jun-2005
Amendment N-000 BL	22-Jul-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	North Shore/LIJ Health System Cyclotron/ Radiochemical Facility
Address:	350 Community Drive Manhasset, New York 11030
Representative:	Thomas Chaly, Ph.D., FAIC email: tchaly@nshs.edu
Telephone:	(516) 562-1042 Fax: (516) 562-1041

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Proposed
b) Non-Proprietary Name (USAN): Fludeoxyglucose F 18 Injection
c) Code Name/# (ONDC only): CAS No. 63503-12-8
d) Chem. Type/ Submission Priority (ONDC only):

- Chem. Type: 5 (new strength)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2); RLD: NDA 20-306

10. PHARMACOL. CATEGORY: Diagnostic PET Radiopharmaceutical

11. DOSAGE FORM: INJECTABLE/Multi-dose aseptic filled, no preservative added. Fill size: 16-17 mL in 20-mL glass vial

12. STRENGTH/POTENCY: 0.74 to 7.40 GBq/mL (20-200 mCi/mL) @ EOS
Shelf life: 12 hrs after EOS

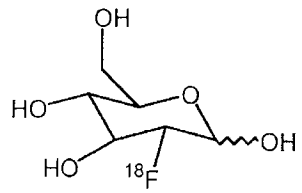
13. ROUTE OF ADMINISTRATION: INTRAVENOUS

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__X__Not a SPOTS product

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

2-Deoxy-2-[^{18}F]fluoro-D-glucose;



$C_6H_{11}{}^{18}FO_5$; M.W. 181.1;
C, 39.78; H, 6.12; F, 9.94; O, 44.16

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]		1	Adequate	17-Aug-05	N/A; LoA provided dated 12-Jan-05
[redacted]	III	[redacted]		4	Adequate	17-Dec-04	N/A; LoA provided

[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
NDA	20-306	Approved and active application for the RLD. Sponsor has given the Agency the right to reference this application. (Different synthesis, formulation & strength than N 21-870)
NDA	21-768	Approved and active application for the RLD. Sponsor has given the Agency the right to reference this application. (Same synthesis and formulation, but different strength than N 21-870)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	N/A	N/A
EES Final Intermediate manufacturer: [redacted]	483 issued – OC recommendation: Acceptable 17-Aug-2005	Inspection dates: Apr 11-14, 2005	Jason Chancey, Chi-DO inspector and Milagros Salazar, CDER Radiochemist
DP manufacturer: North Shore/LIJ Medical Research-Cyclotron, Radichemistry-PET CENTER- Long Island, NY Labeler Code: 13267 Registration (FEI) No.: 3004971261	483 issued, applicant will voluntarily comply. OC recommendation: Acceptable 10-Jun-05	Jun 6-7, 2005	Robert Steyert, NY-DO inspector, Brenda Uratani, CDER, OC and Milagros Salazar, CDER Radiochemist
Pharm/Tox	Not applicable	N/A	N/A
Biopharm	Not applicable	N/A	N/A
LNC	Not applicable	N/A	N/A
Methods Validation	Not applicable	N/A	N/A (USP methods)
OPDRA	Not applicable-No trademark proposed	N/A	N/A
EA	Claim for Categorical Exclusion- Granted	20-Dec-2004	Milagros Salazar, Ph.D.
Microbiology	Approval	02-Aug-2005	James McVey, Ph.D.

19. ORDER OF REVIEW (N/A)

The Chemistry Review for NDA 21-870

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval action based on chemistry manufacturing and controls under section 505 of the Act. In addition, based on acceptable CGMP status found for the manufacturing facilities of the final intermediate, [redacted] after its inspection on Apr 11-14, 2005, under ICH Q7A-GMP Guidance for API. Also, the drug product manufacturer was inspected on June 6 and June 7, 2005 and determined to be in compliance with current applicable standards for PET drug products specifically, USP chapter <823> and FDA PET guidances.

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

None

II. Summary of Chemistry Assessments

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

The drug substance is 2-Deoxy-2-[^{18}F] fluoro-D-glucose and is formed in situ during the manufacture of the drug product. It has a molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.15 daltons, CAS No. 63503-12-8. The drug product Fludeoxyglucose F 18 Injection, 0.74 to 7.40 Gigabecquerels (GBq)/mL (20-200 mCi/mL) at the end of synthesis(EOS), is provided as an isotonic, sterile, pyrogen free, clear, colorless citrate buffered solution. Each mL contains between 0.74 to 7.40 GBq/mL (20-200 mCi/mL) @EOS of no-carrier-added 2-Deoxy-2-[^{18}F] fluoro-D-glucose; 4.5 mg of sodium chloride and 7.2 mg of citrate ions. The pH of the solution is between 5.5 to 7.5. The solution is packaged aseptically as a multiple-dose presentation with a fill size of 16-17 mL in 20 mL glass vial and it does not contain any preservative.

Fludeoxyglucose F 18 Injection is a radiopharmaceutical, containing radioactive F -18 Fluorine with a half life of 109.8 minutes, used for diagnosis purposes in conjunction with Positron Emission Tomography (PET). It is administered by intravenous injection. Due to its short half life Fludeoxyglucose F 18 Injection has a shelf life of 12 hours after it is manufactured.

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

Fludeoxyglucose F 18 Injection, 0.74 to 7.40 GBq (20- 200 mCi/mL), is provided as a multiple –dose package. It is distributed from the [redacted] production site to [redacted] for unit dose [redacted] preparation and under prescription orders. The recommended dose for an adult (70kg) is 185-370 MBq (5-10 mCi) as an IV administration for studies of malignancy, cardiology and epilepsy. Fludeoxyglucose F 18 Injection should be administered after patients have fasted for 4-6 hours. The imaging and identification of regions of the body with abnormal glucose metabolism is based on the biodistribution of the radioactive drug and its gamma radiation emission using PET technology. The final dose to the patient should be calculated using proper decay factors from the time at the end of synthesis (EOS) and measured by a suitable radioactivity calibration system. Fludeoxyglucose F 18 Injection is manufactured for in-house use at the North Shore/LJI Health System- Institute for Medical Research, PET facility and it is also distributed to a local centralized [redacted] radiopharmacy. Fludeoxyglucose F 18 Injection should be used within 12 hours of the EOS when stored at 25 °C (77° F); excursions permitted to 15- 30 °C (59-86 ° F).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval based on the chemistry, manufacturing and control information on 3 commercial size lots which were produced at the maximum proposed strength of 200 mCi/mL. The release and stability testing for the drug product are within the specifications proposed for the USP Fludeoxyglucose F 18 Injection monograph. The quality of the components, the manufacturing process and final controls for this product are adequate to support its identity, strength, purity and quality. In addition, the manufacturing facility for Fludeoxyglucose F 18 Injection was determined to be in compliance with current applicable standards for PET drug products; specifically, USP chapter <823> and FDA PET guidances. The approval of this application is also based on the CGMP acceptable status of the manufacturer of the final intermediate material, [redacted] in compliance with ICH Q7A GMP Guidance for API.

III. Administrative

A. Reviewer's Signature

Milagros Salazar, Ph.D. **Signed**

B. Endorsement Block

ChemistName/Date: Salazar/
ChemistryTeamLeaderName/Date: Leutzinger/ see electronic review
ProjectManagerName/Date: Ngyuyen/ see electronic review

C. CC Block

See electronic review

86 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Milagros Salazar
8/18/2005 01:25:14 PM
CHEMIST
Recommendation: Approval from the CMC standpoint.
PDUFA Due Date: 19-Sep-2005

Eldon Leutzinger
8/18/2005 03:24:58 PM
CHEMIST
I concur with the conclusions and recommendation.