# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208700Orig1s000

# PRODUCT QUALITY REVIEW(S)

# NDA 208700 (Resubmission)
# OPQ Integrated Quality Assessment final
# Review Date: 12/13/2017

| | |
|---|---|
| Drug Product | Lutetium Lu 177 Dotatate / Lutathera |
| Strength | 370 MBq/mL |
| Route of Administration | IV injection |
| Rx/OTC Dispensed | Rx |
| Applicant | Advanced Accelerator Applications |
| US agent, if applicable | N/A |

## Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505b2**

2. **RELATED/SUPPORTING DOCUMENTS:**
   **A. DMFs: See previous IQA**

**Table 1 Drug Master Files (DMFs)**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETE | REVIEWER |
|---|---|---|---|---|---|---|
| | | | | | | |

A. **Other Documents: IND** (b) (4)

3. **CONSULTS: N/A**

**Quality Review Team**

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | John Amartey, Ph.D. | ONDP/DNDAPI |
| Drug Product | John Amartey, Ph.D. | ONDP/Branch VI/Division II |
| Microbiology | Peggy Kriger, Ph.D. | OPQ/OPF/Microbiology |
| Facility | Krishnakali Ghosh, Ph.D. | OPQ/OPF/DIA/B1 |
| Project/Manager (R.Ph) | Thao Vu/Steven Kinsley | OMPT/CDER/OPQ/OPRO/ORDP MI/RBPMBI |
| Application Technical Lead | Eldon E.Leutzinger, Ph.D. | ONDP/Branch VII/Division II |
| Environmental Assessment (EA) | John Amartey, Ph.D. | ONDP/Branch VII/Division II |

**Table 2 Documents**

| DOCUMENT | RECEIPT DATE | DESCRIPTION | Section/reviewer |
|---|---|---|---|
| Resubmission | 7/26/2017 | Application + inspectional documents & FDA 483 | Krishna Ghosh/OPF |
| | | | |

# Executive Summary

## I. Recommendations

**APPROVAL**, based on CMC, Microbiology Product Quality and Facility Inspections

### A. Recommendation and Conclusion on Approvability

N/A

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

N/A

## II. Summary of Quality Assessments

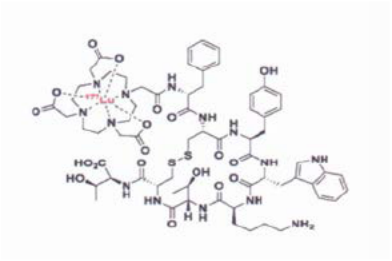
**BACKGROUND**:

The **Drug Product** is a **ready-to-use radiopharmaceutical** contained in a 30 mL single-use glass vial. The vial fits in a lead pig. The pig with the vial is placed in the (b) (4). (b) (4). The dosage form is a solution for intravenous infusion, at a strength of 370 MBq/mL (10 mCi/mL) (b) (4) The shelf-life is 72 hours (b) (4)

A **Complete Response Letter** was issued 12/19/2016 listing multiple clinical issues, as well as deficiencies identified during inspection of the manufacturing facilities. Those facilities included 'Advanced Accelerator Applications (Meldola, Italy; Ivrea, Italy), and IDB Radiopharmacy B.V., the Netherlands.

### A. Drug Substance [USAN Name] Quality Summary

The **Drug Substance** is $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate, a radiolabeled peptide, and has the following molecular structure:



The peptide sequence is d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7), containing 8 amino acids, and has a molecular weight of 1535.6 g/mol. There is a -S-S- disulfide linkage between the two Cys amino acids, connecting the two cysteine amino acids of the peptide together. DOTA is attached to the d-Phe end of the peptide through an amide linkage by utilizing one of the carboxylic acid groups in the ligand, and the free amino group of $H_2N$-d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7). D-Trp$^{4}$ and Lys$^{5}$ each possesses a N-atom that can be protonated, and in NDA 208700, the counter-ion used is trifluoroacetate, two per peptide. After linking DOTA to the peptide, there are remaining 3 carboxylic acid groups and 3 ring N-atoms for binding to $^{177}Lu^{3+}$. The radiolabel ($^{177}Lu^{3+}$) is bound within the DOTA cavity.

The overall process for production of drug substance is as follows. (b) (4)

(b) (4)

B. **Drug Product [Established Name] Quality Summary**

**Product Vial composition** consists of an aqueous solution containing $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate (370 MBq/mL [redacted]), plus excipients (Acetic Acid, Sodium Acetate, Gentisic Acid, [redacted] DTPA and Sodium Chloride). Each vial will contain sufficient volume of solution (20.5 – 25.0 mL) to allow for delivery of 7.4 GBq ± 10% at time of injection. A dose of 7.4 GBq corresponds to 7.4 x $10^3$ MBq, or [redacted] mCi.

**CMC Product Quality**:
In the original submission, there were drug substance issues, [redacted]. For drug product, the most significant issues included lack of information, relative to the batch records. Other drug product issues [redacted] **All issues were resolved, and the final recommendation from CMC was approval**.

**Microbiology Product Quality**:
Similarly, there were multiple Microbiology Product Quality issues [redacted] **All microbiological product quality issues were resolved, and there was an approval recommendation from microbiology**. A determination was made that a review from Microbiology is not necessary, since a recommendation of approval had been made, based on Microbiology Product Quality (Peggy Kriger, email of 9/19/2017).

**Facilities Inspection Status:**
There were 3 manufacturing sites out of 6 recommended for withhold until correction of the 483 observations are complete. All 483 issues have been addressed, and no re-inspection per the resubmission is needed – by determination of Krishnakali Ghosh, Ph.D. (OPQ/OPF/DIA/B1). **On**

**review of the application (Krishna Gosh, OPQ/OPF/DIA/BI), including the inspectional documents and responses to the FDA 483, a determination was made (OPF) that there are no outstanding manufacturing or facility risks preventing the approval of the NDA.**

C. **Summary of Drug Product Intended Use**

| | |
|---|---|
| **Proprietary Name of the Drug Product** | Lutathera |
| **Non Proprietary Name of the Drug Product** | ($^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate) solution for intraveneous infusion |
| **Non Proprietary Name of the Drug Substance** | $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-Octreotate |
| **Proposed Indication(s) including Intended Patient Population** | Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults |
| **Duration of Treatment** | N/A |
| **Maximum Daily Dose** | N/A |
| **Alternative Methods of Administration** | N/A |

D. **Biopharmaceutics Considerations**

1. BCS Classification: N/A
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies: N/A
   - Biowaiver Requests
   - PK studies
   - IVIVC

E. **Novel Approaches**
N/A

F. **Any Special Product Quality Labeling Recommendations**
N/A

G. **Life Cycle Knowledge Information (see Attachment A)**
N/A

**Risk Assessment - Drug Product** (b) (4)

| From Initial Risk Identification | | | Review Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking[1]** | **Risk Mitigation Approach** | **Final Risk Evaluation[2]** | **Lifecycle Considerations/ Comments**** |
| | | RPN < 25 | | RPN < 25 | |

1. Based on CMC and Microbiology Product Quality considerations. Nevertheless, there was a recommendation for withhold on three sites during the original review of the NDA (after a PAI inspection was conducted at the sites) until there was a satisfactory response to an FDA 483 for these sites.
2. Overall Risk Assessment continues to be Low (RPN < 25), based on no new CMC issues uncovered, along with the standing decision of approval by Microbiology Product Quality (no review of resubmission necessary). Additionally, based on a review of the application (Krishna Gosh, OPQ/OPF/DIA/BI) inspectional documents and responses to the FDA 483, a determination was made (OPF) that there are no outstanding manufacturing or facility risks preventing the approval of the NDA.

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E. Leutzinger -S

Digitally signed by Eldon E. Leutzinger -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054329, cn=Eldon E. Leutzinger -S
Date: 2017.12.13 15:13:52 -05'00'

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