CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208700Orig1s000

PRODUCT QUALITY REVIEW(S)

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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

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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

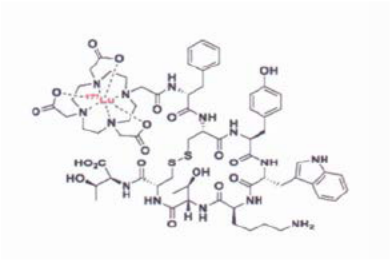
BACKGROUND:

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)

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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**

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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
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