

**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:

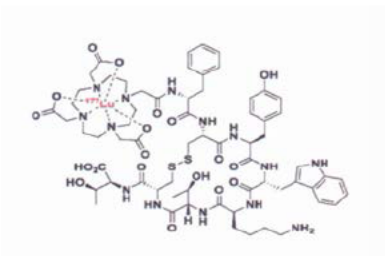
The Drug Product is a **ready-to-use radiopharmaceutical** contained in a 30 mL single-use glass vial. The vial fits in a lead pig. The pig with the vial is placed in the (b) (4). The dosage form is a solution for intravenous infusion, at a strength of 370 MBq/mL (10 mCi/mL) (b) (4).

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 -DOTA⁰-Tyr³-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 **H₂N**-d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7). D-Trp⁴ and Lys⁵ 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 $^{177}\text{Lu}^{3+}$. The radiolabel ($^{177}\text{Lu}^{3+}$) 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 $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ (370 MBq/mL (b) (4)), plus excipients (Acetic Acid, Sodium Acetate, Genticic Acid, (b) (4) 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 \pm 10% at time of injection. A dose of 7.4 GBq corresponds to 7.4×10^3 MBq, or (b) (4) mCi.

CMC Product Quality:

In the original submission, there were drug substance issues, (b) (4)

(b) (4). For drug product, the most significant issues included lack of information, relative to the batch records. Other drug product issues (b) (4)

(b) (4) **All issues were resolved, and the final recommendation from CMC was approval.**

Microbiology Product Quality:

Similarly, there were multiple Microbiology Product Quality issues (b) (4)

(b) (4) **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 intravenous 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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